

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

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GALDERMA LABORATORIES, L.P. and TCD ROYALTY SUB LP	:	Civil Docket 21-CV-1710
	:	
V.	:	Trial Day One
	:	Morning Session
LUPIN INC. and LUPIN LIMITED	:	Civil Bench Trial

BEFORE THE HONORABLE STEPHANOS BIBAS

James A. Byrne U.S. Courthouse
601 Market Street
Philadelphia, PA 19106
January 9, 2024 at 8:30 a.m.

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(Tuesday, January 9, 2024 at 8:30 a.m.)

THE COURT: Good morning. This is the United States District Court for the District of Delaware. And we're in Case Number 21-CV-1710. Galderma Laboratories versus Lupin.

Plaintiffs' counsel, please enter your appearances.

MR. TIGAN: Good morning, Your Honor. My name is Jeremy Tigan. I'm with Morris, Nichols in Wilmington on behalf of the Plaintiffs. I am joined by my co-counsel today from the Cahill Gordon firm. At counsel table I have Gerald Flattmann and Andrew Cochran, and our broader team is in the back. Our client representatives are here as well, David Banchik and Alyssa Klapper.

THE COURT: Good morning. And for the defense?

MS. HANEY: Good morning, Your Honor. Megan Haney from Phillips, McLaughlin & Hall in Delaware. And I am joined today by Bill Rakoczy, Joe Jaros, Katie Boda, and Adrienne Rose, all from Rakoczy, Molino, Mazzochi, Siwik in Chicago. And our representative is also here.

THE COURT: Good morning. So the most important person in the room is the court reporter. Can you hear everything okay? Is the audio working fine for you?

THE COURT REPORTER: Yes.

THE COURT: Please, if you have any problems, don't hesitate to speak up, raise your hand, or go over things again to make sure we've got a good record.

08:31:26AM 1 And so we have a 10-hour per side civil bench trial and
08:31:36AM 2 we're starting now. We will take a midmorning break, 15 minutes.
08:31:41AM 3 we'll take a lunch break of no more than an hour. we'll take
08:31:45AM 4 another midafternoon break. we'll adjust the closing time to
08:31:49AM 5 what makes sense rather than breaking in the middle of a witness
08:31:53AM 6 or starting a witness for 5 or 10 minutes, have some flexibility.
08:31:56AM 7 Let's see if we can get this wrapped up in 3 days. I believe
08:31:59AM 8 both -- each side wants to present an opening statement.

08:32:03AM 9 Are there any preliminaries before we get to openings?

08:32:09AM 10 MR. JAROS: Yes, Your Honor. We had two objections to
08:32:11AM 11 Plaintiffs' opening exhibits under the pretrial order. We are to
08:32:15AM 12 make those before their statement begins.

08:32:18AM 13 THE COURT: Okay. Great. So we have to deal with that
08:32:21AM 14 substantively. Procedurally or mechanically, for your tech
08:32:27AM 15 people, are there any -- I take it that any exhibits that you're
08:32:30AM 16 presenting are going to show on that screen as well as these
08:32:35AM 17 screens? we'll certainly let you know if there are any issues
08:32:40AM 18 with that.

08:32:41AM 19 why don't you remind me of the substance of your
08:32:43AM 20 objections to the exhibits. These are demonstrative exhibits;
08:32:47AM 21 correct?

08:32:48AM 22 MR. JAROS: They are. So they are Plaintiffs' opening
08:32:50AM 23 statement demonstratives. And we have not filed these with the
08:32:53AM 24 Court. They were exchanged last evening --

08:32:53AM 25 THE COURT: Right.

08:32:54AM 1 MR. JAROS: -- so I can address those.

08:32:56AM 2 THE COURT: Please.

08:32:57AM 3 MR. JAROS: May I use the podium?

08:32:59AM 4 MR. FLATTMANN: Your Honor, if it would be helpful, I
08:33:01AM 5 can hand a full set of exhibits up to the Court so that --

08:33:05AM 6 THE COURT: Please do.

08:33:05AM 7 MR. FLATTMANN: -- you can follow along.

08:33:07AM 8 THE COURT: It would be very helpful if you have a
08:33:10AM 9 binder with a set of exhibits or anything like that to hand up.
08:33:13AM 10 If there's an extra one for my clerk.

08:33:15AM 11 MR. FLATTMANN: May I approach?

08:33:16AM 12 THE COURT: Please.

08:33:20AM 13 MR. FLATTMANN: Is two sufficient, Your Honor, or would
08:33:22AM 14 you like one for the -- would the court reporter like one as
08:33:22AM 15 well?

08:33:22AM 16 THE COURT: Would the court reporter like one?

08:33:25AM 17 THE COURT REPORTER: If you have an extra one.

08:33:25AM 18 THE COURT: Is there a set for the defense?

08:33:49AM 19 MR. JAROS: May I proceed?

08:33:50AM 20 THE COURT: Yes.

08:33:51AM 21 MR. JAROS: Your Honor, the first of our objections are
08:33:53AM 22 with respect to Plaintiffs' PDX slide 27 and 28. Very simply,
08:34:02AM 23 those refer to a new publication called Schneider. You can see
08:34:06AM 24 the name of that article in italics on slide 27.

08:34:11AM 25 In this case, Your Honor, their lead expert identified

08:34:14AM 1 the pH of the stomach as an issue early on. In his opening
08:34:18AM 2 report, he addressed it and cited publications in his reply
08:34:22AM 3 report. Because they got the last word, he addressed it again.
08:34:25AM 4 In deposition, I asked him several questions about that area of
08:34:30AM 5 the case, the pH of the stomach.

08:34:33AM 6 In response to a couple of those questions, he was
08:34:35AM 7 instructed not to answer, with respect to the results of his
08:34:39AM 8 searches for publications with respect to the pH of the stomach.
08:34:45AM 9 He accepted that instruction. And then about a month and a half
08:34:48AM 10 later, we received this publication Schneider in November. So it
08:34:54AM 11 was after the deposition, after the filing of the statements of
08:34:57AM 12 fact with the Court.

08:34:58AM 13 And our position is that's too late. This is well
08:35:01AM 14 within the scope of the subject matter, both his opening and
08:35:04AM 15 reply report. It was addressed in deposition but he was
08:35:07AM 16 instructed not to answer as to what he found. And this
08:35:10AM 17 publication appears to be what he found and was disclosed a month
08:35:15AM 18 and a half later.

08:35:17AM 19 THE COURT: Counsel, why are you instructing your
08:35:19AM 20 witnesses not to respond other than privilege?

08:35:22AM 21 MR. FLATTMANN: My understanding is he was not
08:35:24AM 22 instructed not to respond, Your Honor, when he was asked
08:35:27AM 23 questions about cited literature, which noted that the pH of the
08:35:32AM 24 stomach under the appropriate conditions would be about 4.5. He
08:35:38AM 25 relied on an article, in fact, and this is simply a second

08:35:42AM 1 article. He was asked whether there were any other articles.
08:35:45AM 2 And this is one that he found later after the deposition, after
08:35:47AM 3 being asked whether or not he was aware of any other cited
08:35:50AM 4 literature.

08:35:52AM 5 THE COURT: What I will do is I'll take it under
08:35:53AM 6 advisement. If by the break -- and by the way, I'm going to try
08:35:56AM 7 to not deal with these issues during the flow of the testimony
08:35:59AM 8 but at the breaks. But if you want to point me to where in the
08:36:02AM 9 deposition he was instructed not to answer anything like that, if
08:36:05AM 10 you've got a transcript, it should be in the transcript. And you
08:36:09AM 11 can show that to me.

08:36:11AM 12 MR. JAROS: Yes, Your Honor. We have the transcript
08:36:12AM 13 ready. We can put it on the screen.

08:36:14AM 14 THE COURT: Please.

08:36:15AM 15 MR. JAROS: So focusing first on Page 55, Line 17. I
08:36:21AM 16 asked their expert, Dr. Rudnic. "In preparing your opinions in
08:36:26AM 17 this case and the Lupin case, did you search for peer reviewed
08:36:29AM 18 literature stating that a pH of 4.5 is a fasted gastric
08:36:33AM 19 condition?" The instruction was he could answer yes or no based
08:36:37AM 20 on privilege. He answered yes. I asked the question, "Did you
08:36:40AM 21 find any such peer reviewed publications?" And he was then
08:36:44AM 22 instructed not to answer the question and he followed that
08:36:48AM 23 instruction.

08:36:48AM 24 And then I asked, "To be clear, do you believe you
08:36:51AM 25 cited in either of your reports in this case a peer reviewed

08:36:54AM 1 publication, whether the author stated a pH 4.5 is a fasted
08:37:00AM 2 gastric condition?" Answer, "Not in this case."

08:37:04AM 3 Our view is, Your Honor, that was his last chance to
08:37:06AM 4 identify this publication, and it didn't come in until a month
08:37:10AM 5 and a half later so it should be excluded.

08:37:12AM 6 THE COURT: After the expert report deadlines and
08:37:16AM 7 rebuttal reports?

08:37:17AM 8 MR. JAROS: Yes. So this is his deposition came in --
08:37:19AM 9 this is September 1. We received this publication in November.

08:37:22AM 10 THE COURT: Okay. That's untimely. What's your
08:37:24AM 11 response?

08:37:24AM 12 MR. FLATTMANN: Your Honor, we can find the
08:37:28AM 13 complimentary part of this transcript, but he did talk about peer
08:37:31AM 14 reviewed literature in this very same deposition, including the
08:37:35AM 15 Kalantzi article.

08:37:36AM 16 THE COURT: Okay. But not the Schneider one?

08:37:38AM 17 MR. FLATTMANN: He did not mention that during his
08:37:39AM 18 deposition. He did find that subsequent to his deposition upon
08:37:43AM 19 being asked these questions about the cited literature in which
08:37:45AM 20 promptly produced to Lupin in this case. Also, it's an article
08:37:51AM 21 that we would potentially intend to use on cross-examination in
08:37:55AM 22 this case for the very same point.

08:37:57AM 23 THE COURT: It does seem like he's already got Kalantzi
08:38:01AM 24 and some other articles may wind up being cumulative and not
08:38:06AM 25 really matter here. Does it matter?

08:38:10AM 1 MR. JAROS: It matters, Your Honor, because I did not
08:38:12AM 2 have the opportunity to cross-examine him on the substance of
08:38:15AM 3 that publication. It's relatively complex. It includes a number
08:38:19AM 4 of graphs. Had I had notice even a couple days before the
08:38:23AM 5 deposition, I could have absorbed it and examined him on it. But
08:38:27AM 6 he had two shots with his opening and reply report and then could
08:38:30AM 7 have disclosed it before the deposition if they had found it.
08:38:34AM 8 And they instructed him not to answer as to what he did find when
08:38:37AM 9 he went to go look for something.

08:38:38AM 10 THE COURT: Why in the world is this privileged?
08:38:41AM 11 What's the plausible basis for finding an article being
08:38:46AM 12 privileged?

08:38:47AM 13 MR. FLATTMANN: Your Honor, I don't think that this
08:38:49AM 14 precise question about whether it's cited literature is
08:38:53AM 15 privileged.

08:38:54AM 16 THE COURT: I am going to bar it. I am going to bar
08:38:56AM 17 it. These kind of games about objections at depositions, I won't
08:39:00AM 18 stand for that.

08:39:02AM 19 MR. FLATTMANN: Your Honor, may we have an opportunity
08:39:03AM 20 at the break to look at the further context in the deposition?

08:39:07AM 21 THE COURT: You may.

08:39:08AM 22 MR. FLATTMANN: I believe there's a valid answer to
08:39:10AM 23 this.

08:39:10AM 24 THE COURT: You may but you shouldn't go around trying
08:39:12AM 25 to block this kind of thing from an expert privilege. It's not

08:39:16AM 1 right. And the discovery timeline depends on moving promptly.
08:39:22AM 2 This is not a good faith basis for privilege. All right. Please
08:39:25AM 3 proceed.

08:39:26AM 4 MR. JAROS: Second objection, Your Honor, is with
08:39:28AM 5 respect to Plaintiffs' demonstrative Slide 20. On that slide,
08:39:33AM 6 there are two parts. If you have it in front of you, we can also
08:39:37AM 7 put it up on the screen. But on the left-hand side, there's a
08:39:40AM 8 bell curve. On the right-hand side, there's text. We have no
08:39:43AM 9 problem with the text. That was disclosed fairly. Our
08:39:47AM 10 problem --

08:39:48AM 11 THE COURT: This is Slide 20, you say?

08:39:50AM 12 MR. JAROS: Yes, Your Honor. We are not objecting to
08:40:00AM 13 the text on the right. That was disclosed. On the left, there
08:40:03AM 14 is a bell curve that represents again the same experts theory as
08:40:09AM 15 to the distribution.

08:40:11AM 16 THE COURT: Is there any evidence that this follows the
08:40:13AM 17 normal distribution basis for this?

08:40:17AM 18 MR. JAROS: There is not. And I am not sure that's a
08:40:19AM 19 normal distribution. It was called a bell curve in the
08:40:24AM 20 deposition. So similar concept, Your Honor. This bell curve
08:40:29AM 21 concept was not disclosed in an opening report, not disclosed in
08:40:33AM 22 a reply report. It was simply mentioned in the context of
08:40:35AM 23 deposition when I learned for the first time he had two theories,
08:40:38AM 24 number one, all the beads are bad. Number two, some of the beads
08:40:42AM 25 are bad.

08:40:43AM 1 During the deposition, he dropped the all the beads are
08:40:46AM 2 bad argument and went with the some of the beads are bad. And
08:40:50AM 3 then we received this a couple days ago, a bell curve
08:40:54AM 4 representing that some of the beads are bad. So same thing. I
08:40:58AM 5 did have a chance to examine --

08:41:00AM 6 THE COURT: But he mentioned bell curve?

08:41:02AM 7 MR. JAROS: He used the word bell curve.

08:41:06AM 8 THE COURT: Yeah, this is a close enough approximation
08:41:08AM 9 if I take it as not to scale necessarily. It just visualizes
08:41:14AM 10 what he said there. Now, you are entirely entitled to point out
08:41:19AM 11 how little basis he has for the bell curve. But I will take it
08:41:25AM 12 for what it is. It's not to scale. It's not to -- it's just
08:41:29AM 13 like it's visually representing what he said at the deposition.

08:41:33AM 14 And since it was mentioned at the deposition and
08:41:35AM 15 there's no objection here going into the deposition, I am going
08:41:37AM 16 to allow it. But with an appropriate caveat that I am not
08:41:41AM 17 supposed to understand that this is the precise scale or shape.

08:41:46AM 18 MR. JAROS: I believe I understand, Your Honor. So
08:41:47AM 19 essentially this is a demonstrative. This is a cartoon.

08:41:51AM 20 THE COURT: It's a demonstrative cartoon. It's not
08:41:54AM 21 like I can measure the height and width precise conclusions from
08:41:59AM 22 it.

08:42:00AM 23 MR. JAROS: With that, Your Honor, as pure
08:42:02AM 24 demonstrative, we understand, we will withdraw the objection.
08:42:04AM 25 Thank you.

08:42:05AM 1 THE COURT: Anything else? All right. Plaintiffs
08:42:11AM 2 please begin. Let's start the timer.

08:42:13AM 3 MR. FLATTMANN: Thank you, Your Honor. Gerald
08:42:16AM 4 Flattmann on behalf of the Plaintiffs. Your Honor, this case is
08:42:20AM 5 about the Chang patents that cover the Oracea product. And by
08:42:28AM 6 way of a brief background, Oracea is a once-daily doxycycline
08:42:32AM 7 that's indicated for the treatment of inflammatory lesions,
08:42:39AM 8 papules, and pustules of rosacea in adult patients. Now there's
08:42:39AM 9 no dispute that Lupin's proposed generic product works for that
08:42:44AM 10 indication.

08:42:44AM 11 In fact, the FDA has tentatively approved Lupin's ANDA
08:42:48AM 12 for that very purpose. Now the Oracea patents that are at issue
08:42:56AM 13 in this trial are the Chang patents, specifically the 532 and 740
08:42:59AM 14 patents. And those patents cover Oracea's unique once-daily
08:43:04AM 15 formulation of doxycycline designed to maintain blood levels of
08:43:09AM 16 doxycycline between specific thresholds to achieve the goal of
08:43:12AM 17 providing therapeutic efficacy without antibiotic effects.

08:43:17AM 18 And the way to achieve that goal was to formulate
08:43:22AM 19 Oracea with 30 milligrams of immediate release or IR and 10
08:43:26AM 20 milligrams of delayed release or DR components. And indeed, in
08:43:31AM 21 2002, Galderma's predecessor, CollaGenex Pharmaceuticals,
08:43:40AM 22 commissioned a study to determine doxycycline's absorption window
08:43:40AM 23 in the body. And it tested different ratios, including 40
08:43:44AM 24 milligrams of immediate release product and it conducted in
08:43:51AM 25 silico simulations that through that testing determined that a 30

08:43:54AM 1 to 10 immediate release to delayed release ratio could best
08:43:59AM 2 achieve the inventor's goal of maintaining those blood levels.

08:44:04AM 3 Now, Your Honor, these are battle-tested patents and
08:44:07AM 4 they've been in litigation time and time again.

08:44:10AM 5 THE COURT: Chang patents are 532 and 740?

08:44:13AM 6 MR. FLATTMANN: Yes, Your Honor. There's been over a
08:44:17AM 7 decade of challenges to the Chang patents and emerged unscathed
08:44:22AM 8 every time. So the Mylan case, the first one on this list, went
08:44:25AM 9 to trial back in July of 2011. And in that trial, Judge Stark
08:44:29AM 10 heard several of the very same arguments that Lupin is going to
08:44:32AM 11 attempt in this trial.

08:44:34AM 12 But Mylan was held to infringe the 532 Chang patent.
08:44:40AM 13 And then the original Lupin patent challenges rose or fell on the
08:44:44AM 14 result of the Mylan case.

08:44:46AM 15 THE COURT: But there's no argument that I'm estopped
08:44:48AM 16 or any kind of estoppel that would apply to Defendants or
08:44:52AM 17 anything else. I'm deciding this anew; correct?

08:44:55AM 18 MR. FLATTMANN: That's correct. You are deciding this
08:44:56AM 19 anew on the facts. But you are going to see analogous patterns
08:45:01AM 20 and fact patterns and --

08:45:03AM 21 THE COURT: That's fine if I'm persuaded, but you're
08:45:06AM 22 not arguing that I'm bound.

08:45:07AM 23 MR. FLATTMANN: That's correct, Your Honor. That's
08:45:09AM 24 correct. And in the Sandoz action, Sandoz walked away from the
08:45:13AM 25 litigation and then pulled its Paragraph IV certification.

08:45:15AM 1 Dr. Reddy's dropped its challenges to the Chang patents, and then
08:45:19AM 2 there were several cases against Amneal.

08:45:21AM 3 THE COURT: Did any of this involve any numbers near 22
08:45:24AM 4 and 18?

08:45:24AM 5 MR. FLATTMANN: Well, yes. For instance, in the most
08:45:28AM 6 recent and relevant one, Amneal reformulated its proposed ANDA
08:45:32AM 7 product with attorney help, as Lupin has done here, and it's
08:45:36AM 8 certified under Paragraph IV. Initiating a litigation that was
08:45:41AM 9 tried by Judge Stark back in 2018 and notwithstanding the product
08:45:45AM 10 superficially different look from formulation 38 milligrams in
08:45:52AM 11 that case of doxycycline pellets and doxycycline delayed release
08:45:58AM 12 layer of 2 milligrams. So even a starker difference in some of
08:46:03AM 13 the components.

08:46:04AM 14 Galderma proved infringement under the doctrine of
08:46:08AM 15 equivalents there. And then there was the Sun case which is also
08:46:11AM 16 similar where Sun superficially attempted to design around the
08:46:15AM 17 asserted claims and Sun had formulated a bilayer tablet that had
08:46:24AM 18 26.4 milligrams of doxycycline in one layer and 13.6 milligrams
08:46:27AM 19 in the other.

08:46:28AM 20 And Judge Stark found that Sun's product infringed both
08:46:32AM 21 of the patents literally and under the doctrine of equivalents
08:46:36AM 22 despite the superficial differences just like we see here or
08:46:40AM 23 labeling differences I might call them. Where are we now?
08:46:45AM 24 Lupin's ANDA is latest in the long line of design around these
08:46:49AM 25 asserted claims. And it's just the third in a series of attempts

08:46:52AM 1 to evade the claims of the Chang patent with a cleverly disguised
08:46:59AM 2 a functionally viable product. And I submit to you that you will
08:47:02AM 3 reach the same conclusion as your predecessor in Amneal and Sun
08:47:05AM 4 case when you hear the evidence and the proofs from Lupin's own
08:47:10AM 5 ANDA application to the FDA.

08:47:16AM 6 THE COURT: Lupin is not a predecessor in interest or
08:47:18AM 7 otherwise connected to any of those other Defendants?

08:47:21AM 8 MR. FLATTMANN: Not to my knowledge. You will hear
08:47:24AM 9 testimony from Plaintiffs' expert, Dr. Edward Rudnic. Dr. Rudnic
08:47:28AM 10 is an expert in the invention, design, development, testing,
08:47:32AM 11 manufacture, and commercialization of drug products, including
08:47:36AM 12 pharmaceutical formulations. And he's notably the designer and
08:47:40AM 13 developer of Adderall XR, another well-known and a lot of other
08:47:45AM 14 commercial drug products.

08:47:51AM 15 Your Honor, there's a single issue to be tried in the
08:47:53AM 16 case and that's whether Lupin infringes asserted claims of the
08:47:57AM 17 Chang patent. And in this case, it's about infringement. As we
08:48:00AM 18 know, it's not about invalidity or enforceability.

08:48:03AM 19 THE COURT: And you are not really arguing that there's
08:48:06AM 20 much of a difference between the 532 and 740. These probably
08:48:10AM 21 stand to fall together.

08:48:12AM 22 MR. FLATTMANN: Similar patents. One or two minor
08:48:15AM 23 differences. For instance, some of the claims require enteric
08:48:18AM 24 coating and some don't but otherwise they are essentially the
08:48:21AM 25 same. And notably Lupin's arguments are not going to be anything

new. They have been heard in many other forms and at least those other two cases that I mentioned have been essentially rejected.

Your Honor, Lupin infringes the Chang patents and the evidence will show that their product literally infringes and its product is at least equivalent under the doctrine of equivalents to a once a day 40 milligrams product consistent with 30 milligrams immediate release portion and a 10 milligram delayed release portion.

The evidence will show that Lupin's ANDA product is a result of Lupin's deliberate tests to copy the Chang patents. In fact, Lupin intentionally engineered its product to release about 30 milligrams or 75 percent immediate release and about 10 milligrams or 25 percent at a later time following oral administration.

THE COURT: As I understand it, your case rises or falls on whether I credit that there is, in fact, a second 8 milligrams immediate release portion.

MR. FLATTMANN: Whether or not what they called delayed release has another 8 milligrams of immediate release.

THE COURT: That is the factual issue that I am here to decide.

MR. FLATTMANN: Yes, Your Honor. Yes, Your Honor. Whether that 8 milligrams contributes to the immediate release is part of it. Lupin will argue that because its label states nominally different composition ratio, that its product doesn't

08:49:58AM 1 infringe, the Chang patents and Amneal and Sun, same argument
08:50:03AM 2 that was rejected. So the evidence will show right out of
08:50:07AM 3 Lupin's ANDA that its product release is about 30 milligrams of
08:50:12AM 4 doxycycline immediately from combination of what it calls
08:50:16AM 5 immediate release portion and what it calls its delayed release
08:50:20AM 6 portion. That's really the point here.

08:50:22AM 7 And immediate releases 22 milligrams from so-called
08:50:27AM 8 immediate release portion and about 8 milligrams from its
08:50:29AM 9 so-called delayed release portion, as those terms have been
08:50:33AM 10 construed by this Court. Whatever Lupin labels its delayed
08:50:37AM 11 release portion doesn't change the fact that it functions to
08:50:42AM 12 release.

08:50:42AM 13 THE COURT: I understand this to be a case over the
08:50:44AM 14 facts. I don't understand there to be a real dispute about the
08:50:50AM 15 law or the doctrine of equivalents here. Am I right?

08:50:53AM 16 MR. FLATTMANN: I think you are correct. Nor is there
08:50:56AM 17 a dispute about the construction of the claims as Your Honor and
08:51:00AM 18 your predecessors have construed the claims functionally to
08:51:05AM 19 reflect what actually ends up happening in the body.

08:51:10AM 20 So here is just a mathematical type of representation
08:51:15AM 21 of what we just discussed together. The evidence will show that
08:51:19AM 22 Lupin's ANDA product contains this first pellet which contains
08:51:23AM 23 immediate release doxycycline and second pellet which contains
08:51:27AM 24 both immediate release and delayed release doxycycline. And more
08:51:30AM 25 specifically, it will show that Lupin's second type of pellet or

08:51:35AM 1 what they called delayed release portion is actually composed of
08:51:40AM 2 immediate release and delayed release parts. That's the factual
08:51:43AM 3 question here.

08:51:44AM 4 The immediate release part of the second pellet equals
08:51:49AM 5 8 milligrams, and the delayed release equals 10 milligrams. So
08:51:53AM 6 if you do the math, the sum total of the amount of immediate
08:51:57AM 7 release in Lupin's product is 30 milligrams and the total amount
08:52:00AM 8 of delayed release in Lupin's ANDA product is 10 milligrams. So
08:52:05AM 9 the math doesn't lie ultimately.

08:52:07AM 10 THE COURT: So if 8 of the 18 nominally delayed release
08:52:11AM 11 is functional immediate release, then these numbers add up.

08:52:18AM 12 MR. FLATTMANN: Exactly. In any event, our point is
08:52:24AM 13 that Lupin's product is at least insubstantially different.
08:52:27AM 14 That's where we get to the doctrine of equivalents if we need to
08:52:30AM 15 get there.

08:52:31AM 16 It's insubstantially different from a 30 milligram
08:52:35AM 17 immediate release portion and a 10 milligram release portion as
08:52:41AM 18 claimed. That's because the evidence will show the ANDA product
08:52:43AM 19 performs substantially the same function in substantially the
08:52:45AM 20 same way to achieve substantially the same result.

08:52:48AM 21 THE COURT: Okay. So for other than immediately
08:52:51AM 22 following that's already been construed to be about half an hour
08:52:55AM 23 for the way your theory is that the enteric coat is deliberately
08:53:00AM 24 thin and weak enough to result in functionally released within
08:53:05AM 25 half an hour and then the result is obvious in terms of

bioequivalence.

MR. FLATTMANN: That's exactly correct, Your Honor. So notably the FDA has already tentatively approved Lupin's product as bioequivalence and the evidence will show it's not just bioequivalence. It's bioequivalence because it works in substantially the same way as I think Your Honor has followed the line of the argument in the prior slide which also makes it equivalent under the doctrine of equivalents.

So let's walk through the proofs briefly. The evidence will show that Lupin meets the claim element, 30 milligrams immediate release either literally or under the doctrine of equivalents. And that's because upon ingestion, Lupin's ANDA product immediately releases the 22 milligrams of immediate release. And that's in the portion it calls immediate release. They don't dispute that. So we are at least that far along.

And then Lupin's ANDA product immediately releases about 8 milligrams from its so-called delayed release. And how do we know that? First, the evidence will show that what Lupin calls its delayed release portion was intentionally designed with a weak enteric coat.

And second, the evidence will also demonstrate that Lupin's ANDA product with its weakly-designed enteric coat functions to create a 30 milligram immediate release portion and 10 milligram delayed release portion.

And third, the design and function of Lupin's ANDA

product will demonstrate that it infringes.

Next slide, please.

So as mentioned, Dr. Rudnic will testify about the design of Lupin's ANDA product. He will explain that Lupin made two choices to ensure that its enteric coat prematurely and immediately releases. First, it used methylene chloride in its manufacturing process. And second, it used a remarkably low percent weight gain of the enteric coat stage, very thin coat. And he will testify about how those two manufacturing choices amounted to a compromised and weak enteric coating that leaks.

This is from Lupin's own documents that you will see in the course of Dr. Rudnic's testimony. Lupin's decision to use methylene chloride was deliberate. It's a highly toxic solvent that's virtually outlawed in the United States.

Dr. Rudnic will testify that the properties of methylene chloride, which is a non-aqueous solvent layer, that alternates in Lupin's product with an aqueous solvent layer, is to create a leaky coat.

He will explain how those are not compatible layering processes in manufacturing a drug. He will explain that by layering its drug product that way, Lupin compromises not only the integrity of each of those deposited layers of methylene chloride in the aqueous coat but also the ability of the layers to adhere to one another, including at the interface of those enteric coats. And Lupin did this to ensure that some of the

doxycycline in what it calls its delayed release portion would leak immediately upon oral administration. And it does leak. Now in contrast, for instance, Oracea uses aqueous solvents only.

Here are cross sectional scanning electron microscope images of Oracea compared to samples from Lupin's late manufactured R&D product that show the difference. As you can see, and Dr. Rudnic will testify, Lupin's samples are stratified at the interface between the layers whereas the Oracea product shows no such defect.

Next slide, please.

Dr. Rudnic will further testify that Lupin selected a percent weight gain at the enteric coat stage that was intentionally weak and caused the subset of the pellets to leak. He will explain that the percent weight gain as a measure of how much of the enteric coat is applied to the entire pellet population is very low.

And as it accounts for the entire pellet population, the enteric coat thickness will not be exactly the same for every pellet. The coatings on each pellet will be dictated by a standard distribution curve, and some pellets may receive a satisfactory coat but a subset of them will not and those will leak immediately.

Dr. Rudnic is going to discuss how Lupin's intentional selection of an 18 percent weight gain at the enteric coat stage ensures that the coat will leak and that some of the delayed

08:58:03AM 1 release portion will leak immediately. And simply put, the Lupin
08:58:08AM 2 formulation, Lupin formulated its ANDA product to track Oracea's
08:58:13AM 3 formulation very closely, including coating similar sized pellets
08:58:19AM 4 with the exact same polymer Eudragit. But despite those
08:58:22AM 5 similarities, it used 18 percent weight gain while Oracea uses 30
08:58:28AM 6 percent weight gain.

08:58:30AM 7 Dr. Rudnic will explain, based on the data, how Lupin's
08:58:34AM 8 ANDA shows that an 18 percent weight gain is the thinnest coat
08:58:39AM 9 that Lupin could possibly apply that would not result in
08:58:42AM 10 detectible leakage during the in vitro dissolution test of pH
08:58:47AM 11 1.1, the quality control test. And he will explain that the 1.1
08:58:52AM 12 pH testing is not a physiological relevant set but it is a
08:58:57AM 13 quality control measure that will show whether or not pellets
08:59:00AM 14 will leak.

08:59:03AM 15 He will further explain that in his experience, the
08:59:07AM 16 range of percent weight gains using the polymer are typically
08:59:10AM 17 much higher than 18 percent and more in line with Oracea's 30
08:59:14AM 18 percent.

08:59:16AM 19 Next please.

08:59:18AM 20 Now, Lupin's ANDA product functions to release 30
08:59:20AM 21 milligrams of immediate release and 10 milligrams of delayed
08:59:25AM 22 release. The deposition testimony from Lupin's lead formulator
08:59:29AM 23 and corporate witness, Mr. Avachat, as well as the data in
08:59:33AM 24 Lupin's ANDA will prove this.

08:59:36AM 25 Next, please.

08:59:36AM 1 Notably, all of the data that Dr. Rudnic uses to form
08:59:41AM 2 his opinions are found within Lupin's ANDA which was submitted to
08:59:46AM 3 the FDA and confirmed as accurate by Lupin's lead formulator,
08:59:51AM 4 Mr. Avachat. This is in contrast to what Lupin's experts will
08:59:54AM 5 rely on here which are post hoc testing results from a batch of
09:00:00AM 6 product that Lupin manufactured solely for purposes of this
09:00:04AM 7 litigation and its infringement defense.

09:00:06AM 8 And even Lupin's expert, Dr. Buckton, agrees that the
09:00:11AM 9 batch he relied on was manufactured solely for this litigation.
09:00:14AM 10 It was never submitted to the FDA. It was never reviewed by the
09:00:18AM 11 FDA.

09:00:20AM 12 Not only is that litigation driven batch and the
09:00:24AM 13 results of this testing factually questionable, unreliable, and
09:00:27AM 14 inconsistent with the data submitted to the FDA in Lupin's ANDA,
09:00:32AM 15 it is clearly legally improper under the controlling Federal
09:00:34AM 16 Circuit authority, namely the Sunovion case which we've cited.

09:00:40AM 17 That litigation inspired batch doesn't control the
09:00:43AM 18 infringement inquiry. What Lupin has asked the FDA under oath to
09:00:47AM 19 approve is the subject matter that controls the infringement
09:00:52AM 20 inquiry in determining whether infringement has occurred.

09:00:56AM 21 Next slide, please.

09:00:56AM 22 Indeed, Mr. Avachat even testified that quote, "It
09:01:02AM 23 doesn't matter what we did. What matters is what we filed,
09:01:06AM 24 namely the ANDA." He further testified that Lupin quote, "Did
09:01:11AM 25 whatever was required by the regulation to be equivalent in all

09:01:16AM 1 aspects to Oracea." And he and Lupin succeeded.

09:01:21AM 2 Next, please.

09:01:21AM 3 As the Federal Circuit Authority dictates, the relevant
09:01:27AM 4 data for purposes of determining infringement are the ANDA data
09:01:31AM 5 that were actually submitted. Lupin's own data from its ANDA
09:01:35AM 6 reveal how the product actually functions. Specifically, the in
09:01:39AM 7 vitro dissolution data at the more physiologically relevant pH
09:01:44AM 8 4.5, which is the actual pH upon ingestion as indicated, controls
09:01:49AM 9 and so does the in vivo.

09:01:53AM 10 THE COURT: Mysterious substance that doesn't dissolve
09:01:56AM 11 with a highly acidic 1.1 but somehow dissolves at 4.5?

09:02:01AM 12 MR. FLATTMANN: Well, it's not a mystery because the pH
09:02:03AM 13 1.1 test is simply a quality control test. It uses the most
09:02:08AM 14 extreme possible situation that could ever occur in the body if
09:02:13AM 15 something contacted gastric juice, as opposed to the pH of the
09:02:19AM 16 stomach, which ranges between 2.4 and 4.5, which it hits when
09:02:23AM 17 you've had 240 mLs of water on a fasting stomach.

09:02:29AM 18 So yes, these are releasing at 4.5, which is the actual
09:02:34AM 19 physiological relevant condition. 1.1 is a control test. It's
09:02:38AM 20 an important test but it's a control test, quality control test.

09:02:43AM 21 So in getting to that on page -- Slide 26, please.

09:02:53AM 22 This is the Kalantzi article that I mentioned during
09:02:55AM 23 argument earlier which Dr. Rudnic relied on in his report. And
09:03:00AM 24 he'll explain that the FDA requires drinking 240 milliliters or
09:03:05AM 25 about 8 ounces of water when conducting bioequivalence studies.

09:03:10AM 1 And that's the same amount of water that Lupin used when
09:03:14AM 2 conducting it's fasting bioequivalence protocol. That's not too
09:03:17AM 3 surprising.

09:03:17AM 4 He'll explain how the scientific community articles
09:03:21AM 5 like Kalantzi measured the pH of the fasting stomach under these
09:03:25AM 6 same FDA mandated conditions and found it to be a pH of
09:03:29AM 7 approximately 4.5 immediately after administration.

09:03:38AM 8 Let's go to 28.

09:03:44AM 9 So this is a slide from Lupin's own bioequivalence
09:03:49AM 10 fasting study. And as you can see on the slide, Lupin's fasted
09:03:55AM 11 state bioequivalence study involved the administration of 240 mLs
09:03:59AM 12 of water to patients that fasted overnight, which necessarily
09:04:02AM 13 would result in a gastric condition of pH 4.5, the relevant data
09:04:07AM 14 here.

09:04:08AM 15 Next slide, please.

09:04:10AM 16 Dr. Rudnic will also explain that in the in vitro
09:04:15AM 17 dissolution test data at 4.5, the data that was actually
09:04:19AM 18 submitted to the FDA, that that data supports the 30 to 10 ratio
09:04:24AM 19 here. And as you can see here, the mean release of Lupin's ANDA
09:04:29AM 20 product in this bioequivalence test submitted to FDA, the lines
09:04:33AM 21 overlap each other when you compare Lupin's bioequivalence PK
09:04:38AM 22 values and blood values to Oracea's data. That's not surprising.
09:04:43AM 23 It's a bioequivalence product and it's been approved.

09:04:45AM 24 And that's the same product that was -- that was
09:04:49AM 25 exposed to pH 4.5. Same product and its bioequivalence matches

09:04:57AM 1 right up. After exposure to pH 4.5, the mean release of Lupin's
09:05:02AM 2 ANDA product is exactly 30 milligrams or 75 percent.

09:05:09AM 3 Next slide, please.

09:05:10AM 4 Dr. Rudnic will also explain that the individual data
09:05:13AM 5 from the in vitro dissolution test at pH 4.5 supports a
09:05:18AM 6 composition ratio of 30 to 10. And as you can see, Lupin's
09:05:24AM 7 individual capsule data show release after exposure to pH 4.5 in
09:05:29AM 8 the stomach whereas Oracea's delayed release portions do not.
09:05:32AM 9 And not leaking.

09:05:38AM 10 The data here also show that Lupin - Lupin's ANDA
09:05:41AM 11 Product release is more than just 22 milligrams immediately.
09:05:45AM 12 That additional release to get to that 75 percent mean number in
09:05:49AM 13 yellow, that additional release of 8 milligrams, it has to come
09:05:53AM 14 from somewhere. And it comes from the so-called delayed release
09:05:57AM 15 portion.

09:05:59AM 16 Dr. Rudnic will explain that Lupin's individual capsule
09:06:05AM 17 data present a continuum of release profiles ranging from 55 to
09:06:08AM 18 85 percent at that 30-minute mark that we've been looking at.
09:06:12AM 19 And they rely on that very variability, with some capsules
09:06:18AM 20 bursting and some not, to achieve the mean release profile set by
09:06:21AM 21 the profile here.

09:06:23AM 22 THE COURT: I thought that the definition of
09:06:25AM 23 substantially all is within 30 minutes and yet your slide, 1.029,
09:06:31AM 24 has 120 minutes plus another 30 minutes.

09:06:35AM 25 MR. FLATTMANN: Yes. So the timelines for the in vitro

09:06:39AM 1 dissolution test are not directly comparable to what happens in
09:06:44AM 2 the body. So here you're conducting an experiment. You're
09:06:46AM 3 adding different media at different times in the in vitro
09:06:50AM 4 dissolution experiment.

09:06:51AM 5 THE COURT: I got it. I got it. But you're having to
09:06:53AM 6 translate what from in vitro --

09:06:56AM 7 MR. FLATTMANN: Dr. Rudnic is going to do a much better
09:06:59AM 8 job of explaining that than I can.

09:07:01AM 9 THE COURT: Okay.

09:07:02AM 10 MR. FLATTMANN: Slide 31.

09:07:04AM 11 Dr. Rudnic will testify that the results of the fasted
09:07:09AM 12 state bioequivalence studies of Lupin's ANDA product are
09:07:12AM 13 virtually the same as we saw for the results for Oracea. They're
09:07:17AM 14 undisputed 30 milligram immediate release and 10 milligram
09:07:20AM 15 delayed release composition.

09:07:22AM 16 And the fact that the mean plasma concentrations of
09:07:28AM 17 Oracea and Lupin's ANDA product have substantial overlap, you
09:07:31AM 18 know, considering these data together, with all of the other
09:07:34AM 19 evidence that Lupin submitted to the FDA, and it certified to be
09:07:38AM 20 correct and accurate, shows that Lupin's ANDA product has that
09:07:44AM 21 ratio, 30 to 10.

09:07:45AM 22 Let's put it all together in the context of patents.
09:07:50AM 23 Neither Lupin nor its experts dispute that Lupin's ANDA product
09:07:54AM 24 meets all of the elements of the asserted claims, including the
09:07:58AM 25 elements regarding having an immediate release portion and having

09:08:00AM 1 a delayed release portion. The only dispute revolves around the
09:08:04AM 2 claimed ratio.

09:08:07AM 3 Next, please.

09:08:09AM 4 In the Court's construction of the claimed term
09:08:11AM 5 immediate release supports a finding of infringement because the
09:08:15AM 6 term release imparts the functional limitations of claims, and
09:08:20AM 7 the infringement inquiry must account for how the release impacts
09:08:26AM 8 a subject's steady state blood levels in the body.

09:08:29AM 9 So based on all the evidence, Lupin's ANDA product
09:08:32AM 10 releases 30 milligrams of doxycycline immediately to alter the
09:08:37AM 11 subject's steady state blood levels. And that comes, again, from
09:08:42AM 12 a combination of its 22 milligram immediate release portion and
09:08:46AM 13 the 8 milligrams from the delayed release portion on average.

09:08:49AM 14 Next, please.

09:08:49AM 15 As a result of the immediate release of 30 milligrams
09:08:54AM 16 of Lupin's ANDA product, 10 milligrams of doxycycline function to
09:09:01AM 17 release at a time other than immediately following oral
09:09:05AM 18 administration. That's what's left over. It's just the math.
09:09:08AM 19 And that is, again, consistent with the Sun Court and this
09:09:11AM 20 Court's construction of the term delayed release.

09:09:15AM 21 Now, the term -- claimed term portion as conceptualized
09:09:21AM 22 by the Sun Court and adopted by this Court, also supports a
09:09:23AM 23 finding of infringement because the Sun Court elucidated that the
09:09:28AM 24 term portion was a functional limitation, and in particular the
09:09:31AM 25 term was construed to allow for any part of the claimed

composition to contribute an immediate release or delayed release amount depending on the timing of that release.

So contrary to this and the Court's -- and the Sun Court's understanding of the claim terms, Lupin had cited a different case and attempted to state that it is, in fact, analogous to the Reckitt Benckiser case that they brought to your attention, Your Honor.

But in that case, the Court construed the same term portion, they're completely different contexts, have an entirely different meaning. It construed the term "portion" to be structural and singular whereas in Sun, the Court construed portion to be functional and plural, the exact opposite. So as such, the Reckitt case does not control.

Lupin's ANDA product also infringes the Chang patents under the doctrine of equivalents because it's at least insubstantially different from a composition with a 30:10 ratio.

Next, please.

The evidence will show that the design and function of Lupin's ANDA product result in a 30-milligram immediate release 10-milligram delayed release doxycycline product that is equivalent to the asserted claims.

Lupin's ANDA product also infringes the Oracea -- I'm sorry, the Chang method of treatment claims. There are two representative claims being asserted in this case. Claim 19 of the 740, Claim 15 of the 532, and also Claims 20 and 16,

09:11:14AM 1 respectively, which are the dependent claims. And those claims
09:11:17AM 2 are nearly identical to the composition claims that Your Honor
09:11:20AM 3 has reviewed, except that the product is a method for treating
09:11:25AM 4 rosacea in humans in vivo and physiologically relevant context.

09:11:33AM 5 So Lupin's experts, Dr. Buckton and Ms. Gray, will rely
09:11:36AM 6 on a series of flawed opinions and attempt to show
09:11:40AM 7 non-infringement. Dr. Buckton and Ms. Gray will ask the Court to
09:11:46AM 8 focus solely on cherry-picked litigation inspired in vitro
09:11:50AM 9 dissolution data.

09:11:51AM 10 But the evidence will show that Lupin ignores the
09:11:52AM 11 highly probative pH 4.5 data from its own ANDA. And Lupin's
09:11:57AM 12 experts will also largely ignore the in vitro data that Lupin
09:12:02AM 13 relied on to establish bioequivalence and in so doing will fail
09:12:05AM 14 to account for this Court's functional construction.

09:12:09AM 15 Dr. Buckton and Ms. Gray will place undue weight on in
09:12:14AM 16 vitro dissolution data taken from a brand new 6,000-capsule batch
09:12:19AM 17 which was manufactured solely for this litigation and the
09:12:22AM 18 evidence will show that.

09:12:24AM 19 Dr. Rudnic will explain why that batch is not
09:12:26AM 20 representative of Lupin's ANDA product. And why the in vitro
09:12:31AM 21 dissolution data and Lupin's ANDA, which is based on a 230,000
09:12:36AM 22 capsule batch, about 38 times larger batch, is much more
09:12:41AM 23 reliable.

09:12:41AM 24 Dr. Buckton and Ms. Gray will also rely on a so-called
09:12:45AM 25 hotspot phenomenon to explain the release of doxycycline from

09:12:51AM 1 Lupin's delayed release portions in the pH 4.5 test that we're
09:12:55AM 2 relying on. And the evidence will show that this hotspot
09:13:00AM 3 phenomenon is a figment of their imagination. It doesn't exist
09:13:04AM 4 in the literature in any reliable form.

09:13:06AM 5 In conclusion, Your Honor, the evidence will show that
09:13:09AM 6 Lupin infringes each of these asserted claims of the Chang
09:13:12AM 7 patents. Thank you, Your Honor.

09:13:27AM 8 MR. RAKOCZY: Good morning, Your Honor. William
09:13:28AM 9 Rakoczy for the Lupin Defendants. I want to make sure, Your
09:13:32AM 10 Honor, you have the Lupin slides.

09:13:35AM 11 THE COURT: Yes.

09:13:45AM 12 MR. RAKOCZY: May I proceed, Your Honor?

09:13:45AM 13 THE COURT: Please.

09:13:47AM 14 MR. RAKOCZY: I will briefly preview for the Court what
09:13:49AM 15 the evidence will show regarding the asserted patents and the
09:13:53AM 16 Lupin products. Suffice it to say you will hear a very different
09:13:56AM 17 perspective from me than what you just heard. At the end of the
09:14:00AM 18 day, we submit the evidence will show Lupin's product does not
09:14:02AM 19 infringe. In our affirmative case, we will present evidence on
09:14:05AM 20 what the patents teach, the patents claim, and how Lupin's
09:14:08AM 21 product functions.

09:14:10AM 22 In short, Your Honor, the patents teach very precisely
09:14:14AM 23 how to make the claim composition, how to test it, and how to
09:14:18AM 24 describe it. According to those very precise and clear
09:14:21AM 25 teachings, Lupin's product functions as 22 milligrams immediate

09:14:25AM 1 release and 18 milligrams delayed release, which I will call
09:14:31AM 2 22:18 or the 22:18 IR/DR ratio which is not even close to the
09:14:36AM 3 claimed 30:10 ratio.

09:14:39AM 4 In our rebuttal case, we will show that the so-called
09:14:43AM 5 subset theory is both a contradiction and its been disproven
09:14:47AM 6 definitively. According to that subset theory, Galderma and its
09:14:51AM 7 experts suggest that of the 18 milligrams of Lupin's delayed
09:14:54AM 8 release or DR beads, 8 milligrams will somehow, someway
09:14:59AM 9 immediately and completely release while the remaining 10
09:15:03AM 10 milligrams will work perfectly and continue to delay release as
09:15:07AM 11 intended.

09:15:08AM 12 There's no support for that contradiction, Your Honor,
09:15:11AM 13 no evidence. All of Lupin's DR beads are made the exact same way
09:15:16AM 14 using the same process, using the same ingredients. In fact,
09:15:20AM 15 Lupin uses the same enteric coating that is on Oracea. There is
09:15:24AM 16 no credible evidence that that coating is weak.

09:15:27AM 17 In fact, Lupin used a coating that falls squarely
09:15:30AM 18 within the range allowed in the patents and the testing will show
09:15:35AM 19 that. There's no way to reconcile Galderma's theory, again, that
09:15:39AM 20 somehow 8 milligrams of those DR beads completely and immediately
09:15:43AM 21 fail but 10 milligrams continue to work perfectly.

09:15:47AM 22 But on top of that, we tested that theory. Galderma
09:15:50AM 23 didn't. We tested this pH 4.5 subset theory. We gave Lupin's
09:15:55AM 24 capsules to an independent testing laboratory to see what would
09:16:00AM 25 happen. Galderma conducted no testing in this case on hundreds

of capsules and thousands of beads. We took their theory. We don't agree that this pH 4.5 subset test is a proper test, but we said let's test it and see what happens.

And when we did, the results came back from the independent testing laboratory and it showed no additional immediate release from the DR beads. None. None of those beads failed much less completely and immediately. So there's no support, and we disproved this subset theory.

And with that, Your Honor, all the rest of their case falls, including the blood level theory. They then have a backup theory where they say the blood levels corroborate the ratios because Lupin's ratio is somehow similar to Oracea but that all depends on the subset that somehow there's this subset of 8 milligrams of the DR beads not working.

We disproved that. On top of that, the evidence will show you can't seriously infer composition ratios from looking at blood level.

So Your Honor, we submit at the end of the day, Galderma's infringement theories are not based on science or facts or hard data. They're based on assumption. And their key assumption that somehow Lupin's 22:18 product at pH 1.1 somehow transforms into a 30:10 product at pH 4.5 is not supported, it's wrong, and it's been disproven by our 4.5 pH rebuttal testing.

So we submit we'll be left with one simple truth at the end of this case and that is that using the same test and

09:17:43AM 1 conditions from the prior cases from the Amneal and Sun cases
09:17:47AM 2 that used that pH 1.1 condition to confirm the IR DR ratio there
09:17:53AM 3 will be no general dispute that Lupin's product does not
09:17:56AM 4 infringe.

09:17:56AM 5 And I'd like to emphasize that point again. If we used
09:18:01AM 6 the patent test, the test out of their own patent that was also
09:18:05AM 7 used in the Amneal and Sun litigation, there's no serious dispute
09:18:10AM 8 Lupin's product functions as 22:18. And you don't have to take
09:18:14AM 9 my word for it, Your Honor. We have a slide to prove it. This
09:18:18AM 10 is DDX 1, Slide 3. This is right from Galderma's own statement
09:18:21AM 11 of facts, Paragraph 106.

09:18:23AM 12 The data at pH 1.1, that's the same condition and test
09:18:27AM 13 used in their own patent used in the Amneal and Sun litigation.
09:18:31AM 14 It's also an industry standard test from the FDA, from the US
09:18:37AM 15 Pharmacopeia, which is the standard setting organization for all
09:18:39AM 16 pharmaceuticals in the United States. It's the test they use on
09:18:43AM 17 Oracea.

09:18:44AM 18 At this test, they admit that Lupin's product releases
09:18:47AM 19 approximately 50 percent at 30 minutes and 54 percent at 120
09:18:52AM 20 minutes. And they further admit that's coming from the immediate
09:18:54AM 21 release portion. That equates to a 22 milligram immediate
09:18:59AM 22 release product, 18 milligrams delayed release. Not even close
09:19:03AM 23 to the 30:10.

09:19:05AM 24 With that, Your Honor, I'd like to just highlight the
09:19:08AM 25 few points in our affirmative case, and I'd like to start with

some discussion about the patent. We didn't hear a whole lot of discussion about the patent and the composition ratios. We heard a little bit about blood ratios, nothing about this.

At a very high level here on DDX 1, Slide 5, the summary of the invention says, in yellow, it's a pharmaceutical composition of doxycycline and it consists of an IR, or immediate release component, in purple. I think that's purple. I apologize. It's not showing up well. And in blue, a DR component.

And those can be combined in a unit dosage form at a preferred ratio. And the most preferred ratio in the patent is what you see here, 75 to 25 IR to DR. And that simply means at a 40-milligram dose, 75 percent is IR, 25 percent is DR. And that translates into 30 milligrams IR, 10 milligrams DR, so 75:25 is the same as 30:10.

Now the patents teach the skilled person exactly how to make those components to start with the immediate release or IR, and we have it in its most simplest form here in example 1 on Slide 6. And an easy way to do it is to take a dispersion of doxycycline and polymer and spray it on to a sugar seed or bead. And that makes what the patent calls an IR bead.

That IR bead can then be tested, the patent tells the skilled person exactly how to do it. It's here in Figure 1 on Slide 7, so we will jump to that. This is a figure we didn't hear anything about during their opening. They don't want to

09:20:49AM 1 talk about this at all. This is their own test. And I will say,
09:20:53AM 2 Your Honor, it's highly unusual for a patentee to criticize their
09:20:58AM 3 own test and run away from it. Usually they're dying for the
09:21:01AM 4 Defendant to use their test.

09:21:03AM 5 And that's what we did. This is a dissolution test or
09:21:07AM 6 a release profile test. It's pH 1.1 condition measuring at 10,
09:21:14AM 7 20, 30 minutes, they tested the IR beads and you can see, based on
09:21:17AM 8 that curve, at 10, 20, and 30 minutes, these IR beads release
09:21:22AM 9 virtually all of their drug, as they were intended, designed and
09:21:25AM 10 manufactured.

09:21:28AM 11 The patent also teaches how to make delayed release or
09:21:31AM 12 DR -- this is example 2 on Slide 9. And again, this is a fairly
09:21:35AM 13 simple process where you take the IR bead from the prior example
09:21:40AM 14 and then you spray an enteric or delayed release coating onto it,
09:21:44AM 15 and that's a special coating, Your Honor, that is made to delay
09:21:49AM 16 release in the acidic condition of the stomach and then allow
09:21:54AM 17 release later on in the intestine with a higher pH.

09:21:57AM 18 And here a very simple way to do it is to apply this
09:22:03AM 19 Eudragit L 30 D-55 enteric coating. It's actually the exact same
09:22:09AM 20 coating on Lupin's product and Oracea, the commercial embodiment
09:22:12AM 21 product. So you take that coating, you spray it onto the IR bead
09:22:16AM 22 and now you have a delayed release or DR bead.

09:22:19AM 23 And again, as you can expect, the patent teaches how to
09:22:23AM 24 test for delayed release and it points us to Figure 2. Here we
09:22:28AM 25 have another test Galderma doesn't want to talk about. It's a

09:22:33AM 1 dissolution release profile test, but this is two stages. So
09:22:38AM 2 this starts out at pH 1.1 through 2 hours and then it goes up to
09:22:43AM 3 pH 7.0 in the --

09:22:45AM 4 THE COURT: These are all in vitro tests; right? The
09:22:48AM 5 time is running from the time you put it in a petri dish, not
09:22:52AM 6 from the time --

09:22:52AM 7 MR. RAKOCZY: Correct, Your Honor. These are industry
09:22:54AM 8 standard tests for how you measure both IR and DR. And in the
09:22:59AM 9 first part, the 2 hour at 1.1, that is meant to show you how this
09:23:04AM 10 drug would function upon administration, meaning how would the
09:23:08AM 11 drug dissolve and release from the dosage form upon
09:23:12AM 12 administration. And here in Figure 2, they are testing the DR
09:23:16AM 13 beads. And as you can see, as manufactured and intended, during
09:23:20AM 14 the first 2 hours of pH 1.1 DR beads are releasing no drug
09:23:25AM 15 whatsoever.

09:23:26AM 16 But then when it switches over to the higher pH that
09:23:29AM 17 you would see in the intestine the DR bead is releasing
09:23:34AM 18 substantially all of its drug as you would expect as it was
09:23:36AM 19 manufactured.

09:23:37AM 20 And then finally, we have the combination capsule.
09:23:40AM 21 Here on slide 12 this is example 3. And put simply, you take the
09:23:45AM 22 ratio of the beads that you want and you fill the capsule. The
09:23:50AM 23 most preferred ratio in this example, again, is the 75 percent IR
09:23:54AM 24 or 30 milligrams IR and 25 milligrams DR -- or I'm sorry. 10
09:24:01AM 25 milligrams DR or 25 percent DR and you put those into the

capsule.

And we have a test for that as well. The patent points us to Figure 3 as we see here on Slide 13 and in Figure 3, that's exactly what they do, Your Honor. They take that 40 milligram capsule and they put it into the two-stage test and at pH 1.1 at the 1-hour and 2-hour time points, you see that this capsule is releasing approximately 75 percent immediately or 75 percent IR as they put into it and as it was manufactured. And then it's releasing the remainder of its drug thereafter in the higher pH or the 25 percent DR. So this test is confirming that, in fact, upon administration, this capsule is releasing as it was intended to, as it was made.

Now, let's very briefly look at the asserted claims and how these concepts are used. I won't belabor this, we've already looked at it. But again, Claim 1, an oral pharmaceutical composition consisting of in purple 30 milligrams IR and 10 milligrams DR. And the broadest claims, Your Honor, are about 30 to 10 and that makes for a variance of a 10 percent at most, so our broadest claims are about 30:10. And something I want to emphasize here.

This 30:10 composition ratio, it's obviously a separate and independent obligation or requirement of the claims for all purposes including infringement. And it was also critical to the issuance of these claims. The applicants originally tried for a claim to any composition that gives the claim steady state blood

1 levels. A hard stop. No dose limitation. No component
2 limitation. No ratio limitation. And we see that broad Claim 1
3 here on Slide 18. This goes all the way back to April of 2003.
4 Claim 1, any composition that hits the blood levels. Full stop.
5 Claim 7 did have the IR/DR ratio, but it was extremely broad,
6 about 99 to 1 to 70:30 so basically covering anything.

7 They couldn't get these claims. The patent office
8 never allowed these in this form. They were rejected and through
9 a series of amendments, here on Slide 19, we finally see the
10 30:10 IR/DR claims that we know today. But even these claims
11 were not originally allowed. And that's because the patent
12 examiner found a 23 to 16 IR to DR composition in the prior so
13 she rejected the claims on the ground that 23 to 16 IR to DR was
14 about 30 to 10.

15 The applicants obviously cried foul and said that can't
16 be the case because 23 to 16 is over 30 percent different from
17 about 30:10. And told the examiner in no case would the skilled
18 person think a variance of 30 percent or greater is accomplished
19 by about. So basically they said, 23:16 not covered by our
20 claims. They disclaimed that. And the only reason I bring it
21 up, Your Honor, is because we believe the evidence will show
22 Lupin's product is 22:18. That is even further away from 30:10
23 than 23:16. So if we prove, and we believe we will, Lupin is
24 22:18, that does not infringe 30:10 literally or under any
25 reasonable scope of equivalence.

09:27:40AM 1 I'd like to just touch upon what the evidence will show
09:27:42AM 2 on Lupin's product. I believe much of this should not be in
09:27:46AM 3 serious dispute beginning with paragraph 61 of Galderma's
09:27:51AM 4 statement of facts.

09:27:52AM 5 THE COURT: By the way, that ratio then distinguishes
09:27:54AM 6 your case from the other precedents when you mentioned 26 and
09:27:59AM 7 some other numbers that many of those were not within this as you
09:28:05AM 8 read it safe harbor.

09:28:09AM 9 MR. RAKOCZY: Correct, Your Honor. We're far, far away
09:28:10AM 10 from the prior cases and we're far away even from the the 23:16
09:28:13AM 11 and the prosecution history. Galderma admits, Your Honor, that
09:28:18AM 12 the Lupin product is, in fact, designed and manufactured as a 55
09:28:21AM 13 percent, 45 percent IR to DR product. In short, Lupin takes 55
09:28:27AM 14 percent IR beads and then they set aside 45 percent which they
09:28:35AM 15 then enteric coat to make DR beads. So it's a 55:45 ratio
09:28:39AM 16 product. And that translates into 22 milligrams immediate
09:28:42AM 17 release 18 milligrams DR.

09:28:44AM 18 So 55:45 is 22:18. And that's exactly how the Lupin
09:28:51AM 19 product functions according, again, to industry standard tests,
09:28:56AM 20 the tests from the patent, the tests that they use on Oracea.
09:28:59AM 21 Here on Slide 23, we have a couple things on the left. We have
09:29:04AM 22 the Court's constructions of IR portion and DR portion. And
09:29:09AM 23 again, IR portion being that functional part, any part that
09:29:13AM 24 releases immediately upon administration with no delayed effect.

09:29:17AM 25 And the DR portion being functional that which delays

09:29:21AM 1 release to a time other than immediately following
09:29:26AM 2 administration. On the right what we've done is we have a patent
09:29:29AM 3 Figure 3. We have the dissolution test and we have two sets of
09:29:34AM 4 data. In black, that graph is the 30:10 claimed composition.
09:29:39AM 5 And as we saw earlier, you can see that in pH 1.1 it is releasing
09:29:45AM 6 approximately 75 percent of its drug as expected. That's the way
09:29:49AM 7 it was made, 75:25 IR to DR and it's releasing the rest of the
09:29:54AM 8 drug thereafter.

09:29:56AM 9 In green, we plotted the actual Lupin ANDA exhibit
09:30:00AM 10 batch data. This is the data actually from the ANDA submitted to
09:30:04AM 11 the FDA. This is illustrative, Your Honor. There are dozens of
09:30:10AM 12 tests with this exact same data submitted to the FDA, approved by
09:30:14AM 13 the FDA, it's unchallenged in this case. Galderma has done no
09:30:18AM 14 testing. This data clearly shows that at pH 1.1, the capsule is
09:30:25AM 15 releasing approximately 55 percent of its drug or 22 milligrams
09:30:28AM 16 immediate release, and then releasing the remainder at the higher
09:30:32AM 17 pH. This data is undisputed. No matter how we parse or analyze
09:30:38AM 18 this data, it's all the same.

09:30:40AM 19 Here on Slide 24 this is one example of the actual raw
09:30:44AM 20 numbers that went into the green plot on Slide 23. Slide 24, we
09:30:52AM 21 have the raw numbers. And you can see at 30 minutes, the Lupin
09:30:56AM 22 capsule is releasing 53 percent at 60 minutes, 55 percent at 120
09:31:00AM 23 minutes, 56 percent. So an average of 55 percent release in
09:31:06AM 24 those time points, that is 22 milligrams immediate release. The
09:31:10AM 25 Lupin product is functioning according to all of the tests in the

09:31:14AM 1 ANDA as 22:18.

09:31:17AM 2 You can see the stark contrast between the 30:10
09:31:22AM 3 product and Lupin's ANDA exhibit batches here on slide 25. In
09:31:30AM 4 purple, we have Oracea, the 30:10 product. Again, you can see
09:31:32AM 5 releasing immediately around 75 percent or 30 milligrams. You
09:31:37AM 6 see the Lupin products blue, red, and green. Those are
09:31:41AM 7 composites of all of the ANDA exhibit batch data. And again,
09:31:45AM 8 releasing starting at 30 minutes and going on anywhere from 50 to
09:31:52AM 9 55 percent. So 30 -- excuse me, 22 milligrams IR, 18 milligrams
09:31:59AM 10 DR.

09:32:00AM 11 And there, Your Honor, we believe the evidence will
09:32:03AM 12 show in the end Lupin's product is designed, made, tested and
09:32:07AM 13 properly labeled as 22:18. I point this out on slide 26 because
09:32:12AM 14 this is a portion of Lupin's label where it clearly says each
09:32:17AM 15 capsule contains 22 milligrams immediate release pellets and 18
09:32:22AM 16 milligrams delayed release pellets.

09:32:27AM 17 The FDA has approved this label and this ratio. They
09:32:28AM 18 have approved it based on dozens of industry standard tests from
09:32:32AM 19 the ANDA. They have approved it because it is true and accurate.
09:32:37AM 20 Again, those results are unchallenged and the product has been
09:32:41AM 21 approved by the FDA as 22:18 as properly labeled as 22:18.

09:32:47AM 22 THE COURT: Friend on the other side says it's based on
09:32:50AM 23 a cherry picked subset of capsules that were produced.

09:32:55AM 24 MR. RAKOCZY: So, Your Honor, we're talking about two
09:32:56AM 25 different sets. So the data we looked at slide 23 and slide 24,

09:33:02AM 1 this is not what he's referring to as cherry picked data. This
09:33:06AM 2 is data right out of the ANDA submitted to the FDA.

09:33:09AM 3 what he's referring to is in rebuttal when they came up
09:33:18AM 4 with this pH 4.5 theory, we thought to ourselves what's the best
09:33:23AM 5 way to test whether Lupin's DR beads release in 4.5. We thought,
09:33:30AM 6 why wouldn't you test them in pH 4.5? we gave them hundreds of
09:33:34AM 7 capsules and thousands of beads. They tested none. Matter of
09:33:39AM 8 fact, when we asked their expert at the dep, why didn't you test
09:33:42AM 9 anything? He was instructed not to answer for privilege and he
09:33:44AM 10 refused to answer.

09:33:45AM 11 All we know is they've disclosed no testing in this
09:33:49AM 12 case whatsoever. If they did testing, we don't know about it,
09:33:52AM 13 they didn't disclose it. But we thought we're going to test this
09:33:55AM 14 theory. We disagree that this is the proper test to do. So what
09:33:59AM 15 we did was, because our exhibit batch samples had expired
09:34:05AM 16 already, and we thought they'd criticize that if we tested those,
09:34:09AM 17 so we had Lupin make a new smaller batch of ANDA product.

09:34:14AM 18 Mr. Avachat, the head of R&D at Lupin, will be here to
09:34:18AM 19 testify that these 6,000 cap capsules were made the same way as
09:34:21AM 20 the ANDA product. They are the ANDA product. They were made
09:34:24AM 21 according to the same processes, they contain the same
09:34:27AM 22 ingredients and the same amounts. We then took those capsules
09:34:30AM 23 and gave them to an independent laboratory. They tested them and
09:34:34AM 24 this is what they saw in pH 4.5: 55.4 percent release from
09:34:40AM 25 Lupin. That's all from the IR portion. None of the DR beads

09:34:45AM 1 failed, much less completely and immediately, as their theory
09:34:51AM 2 posits. So we believe this completely disproves their pH 4.5
09:34:56AM 3 theory.

09:34:57AM 4 Putting that aside, Your Honor, I don't want the Court
09:35:01AM 5 to ignore the fact that using the patent test, that's what we're
09:35:08AM 6 looking at. The patent test, this is the test from Amneal, the
09:35:09AM 7 test from Sun. This is actually FDA's test, USP test and
09:35:15AM 8 Oracea's test. These capsules perform as 22:18 and you will hear
09:35:21AM 9 no challenge to these results, not a single challenge. They
09:35:25AM 10 agree with these results.

09:35:26AM 11 So we believe that the evidence shows Lupin is 22:18
09:35:32AM 12 according to unchallenged dozens of tests submitted to the FDA
09:35:38AM 13 and even if we want to throw the capsules in pH 4.5 they are
09:35:45AM 14 showing 55 percent release, immediate release, 22:18. So no
09:35:50AM 15 matter how you look at it, these don't infringe and, Your Honor,
09:35:54AM 16 I want to pause and emphasize that again.

09:35:56AM 17 If they really thought this pH 4.5 theory had legs,
09:36:00AM 18 they could have tested it. They could have taken the capsules
09:36:03AM 19 and the beads and put it in pH 4.5 like we did. We went out of
09:36:07AM 20 our way to make more capsules to try and give them the benefit of
09:36:13AM 21 the doubt and test their theory and now they're complaining about
09:36:15AM 22 that. They tested nothing. We gave them the original ANDA
09:36:19AM 23 samples, they didn't test them. We gave them samples of this new
09:36:23AM 24 batch. They didn't test them. We did and we disproved their 4.5
09:36:28AM 25 theory.

09:36:30AM 1 So with that, Your Honor, I will end as I began and
09:36:35AM 2 that is if you use the test from the patent and the test from the
09:36:40AM 3 prior cases, we submit there's no genuine dispute that Lupin
09:36:45AM 4 product functions as 22:18 or 22 milligrams immediate release 18
09:36:51AM 5 milligrams delayed release. That's not even close to 30:10
09:36:55AM 6 literally or under any reasonable scope of equivalence.

09:37:00AM 7 Before I step down, Your Honor, I would like to briefly
09:37:03AM 8 introduce the live witnesses we will call. The first will be
09:37:06AM 9 Mr. Makarand Avachat. He is the executive vice president of
09:37:11AM 10 pharmaceutical R&D, and he oversaw the development of the Lupin
09:37:15AM 11 product.

09:37:15AM 12 The second is Ms. Vivian Gray, an expert in dissolution
09:37:18AM 13 testing of pharmaceutical compositions.

09:37:20AM 14 And the third is Dr. Graham Buckton, an expert in
09:37:23AM 15 formulation development and pharmaceutical composition testing.
09:37:27AM 16 Thank you, Your Honor.

09:37:28AM 17 THE COURT: Wonderful. Can you give me just a vague
09:37:31AM 18 estimate of how long you think each of these live witnesses will
09:37:34AM 19 take?

09:37:37AM 20 MR. RAKOCZY: Mr. Avachat will be approximately 50
09:37:40AM 21 minutes to an hour. Ms. Gray will be about 45 minutes, 50
09:37:52AM 22 minutes. And then Dr. Buckton will be much longer, 3 to 3 and a
09:37:59AM 23 half hours.

09:38:01AM 24 THE COURT: All right. Very good. Thank you for that.
09:38:07AM 25 Plaintiff proceed.

09:38:12AM 1 MR. COCHRAN: Your Honor, Plaintiffs call Dr. Edward
09:38:16AM 2 Rudnic.

09:38:18AM 3 THE COURT: Please. Do you have a rough estimate of
09:38:25AM 4 the length of direct examination here?

09:38:29AM 5 MR. COCHRAN: we will be approximately 2 hours, Your
09:38:29AM 6 Honor.

09:38:49AM 7 MR. RAKOCZY: Under the pretrial order we were supposed
09:38:51AM 8 to raise objections before the examination starts. I have just
09:38:55AM 9 several to some exhibits. I think some have been taken care of
09:38:58AM 10 already.

09:38:59AM 11 THE COURT: why don't you hand up those books and then
09:39:02AM 12 the Plaintiff will hand out the books for the witness and then I
09:39:05AM 13 can look at the exhibits that we're talking about. It will help
09:39:08AM 14 me while Mr. Rakoczy is discussing them. Review those before we
09:39:18AM 15 swear the witness.

09:39:18AM 16 MR. RAKOCZY: Your Honor, may I approach?

09:39:33AM 17 THE COURT: what exhibits would you like to draw my
09:39:35AM 18 attention to?

09:39:36AM 19 MR. RAKOCZY: Yes, Your Honor, four exhibits.

09:39:39AM 20 THE COURT: we've have already talked about Schneider.

09:39:43AM 21 MR. RAKOCZY: Four slides that were Schneider and those
09:39:46AM 22 are PDX-2.13, 14, 66 and 67. And so unless Your Honor would like
09:39:54AM 23 to hear anything else on Schneider, I can move on to the other
09:39:58AM 24 ones. Four of these slides, PDX-2.53, 55, 61, and 62 again.

09:40:06AM 25 THE COURT: Sorry. Are those slide books that will

09:40:10AM 1 help me to see the slide books, too, because he's referring to
09:40:15AM 2 them by slide? So go over the first one.

09:40:25AM 3 MR. RAKOCZY: Schneider was PDX-2, slide 13, 14, 66,
09:40:41AM 4 and 67.

09:40:45AM 5 THE COURT: Some of these Kalantzi.

09:40:52AM 6 MR. RAKOCZY: Yes, we are not objecting to Kalantzi.

09:40:58AM 7 THE COURT: To the extent these are substantiated by
09:41:00AM 8 Kalantzi that's fine. What was the next?

09:41:02AM 9 MR. RAKOCZY: The next set were more of the bell curve,
09:41:06AM 10 Your Honor.

09:41:07AM 11 THE COURT: Which again, I'm okay allowing as a
09:41:09AM 12 demonstrative cartoon now understood not to scale.

09:41:15AM 13 MR. RAKOCZY: My issue now, Your Honor, is it changed.
09:41:19AM 14 It started -- if you look at PDX-2, slide 53, they now have
09:41:24AM 15 started to add numbers to it on both.

09:41:29AM 16 THE COURT: I don't see a number on 53.

09:41:32AM 17 MR. RAKOCZY: I'm sorry, Your Honor. Slide 55 and 56.
09:41:37AM 18 They're now adding numbers and a cross hatch graph.

09:41:41AM 19 THE COURT: This is just -- appears to be speculation.

09:41:48AM 20 MR. RAKOCZY: We submit it is. It's one thing in our
09:41:51AM 21 view to mention a bell curve, it's another to attempt to start to
09:41:54AM 22 make -- what appears to be implying actual distributions here.

09:42:01AM 23 MR. COCHRAN: Your Honor, these are the averages. The
09:42:04AM 24 Lupin 18 percent Oracea --

09:42:07AM 25 THE COURT: I think the witness is testifying to this.

09:42:09AM 1 I think it's more a question of whether the witness has any
09:42:12AM 2 foundation or whether it's speculation as to whether these
09:42:16AM 3 numbers belong at these peaks.

09:42:19AM 4 MR. RAKOCZY: well, he can -- Your Honor, the 18
09:42:20AM 5 percent and the 30 percent are the average coating weights on the
09:42:24AM 6 products, but what he's done is he's put that at the top and then
09:42:28AM 7 drawn extremely wide bell curves of distribution of -- between
09:42:34AM 8 weakly coated and more robustly coated and then put the cross
09:42:38AM 9 hatching --

09:42:39AM 10 THE COURT: But then he's suggested that the
09:42:41AM 11 distributions barely overlap in the middle. And so I'm not going
09:42:44AM 12 to treat the overlap that's for which it doesn't seem like
09:42:50AM 13 there's a basis. Like, yes, these are average coating weights,
09:42:53AM 14 but as to how that plays out, how far apart the curves are, etc.,
09:42:59AM 15 you know, there's a foundation -- there's going to be a
09:43:01AM 16 foundation issue.

09:43:04AM 17 MR. COCHRAN: There's a -- Dr. Rudnic, I'll be asking
09:43:05AM 18 him about these curves. These are exemplary curves and he'll be
09:43:11AM 19 testifying.

09:43:11AM 20 THE COURT: Okay. We're going to use this as a
09:43:13AM 21 demonstrative and talk about the foundation for it.

09:43:13AM 22 what else?

09:43:17AM 23 MR. RAKOCZY: My last two objections, Your Honor, are
09:43:19AM 24 just to, for the record, I want to renew them so that they are
09:43:21AM 25 not waived. And that is Slide 68 and 69 are the subject of our

09:43:28AM 1 MIL or motion in limine Number 1. And I just want to put on the
09:43:30AM 2 record that we renew our motion in limine as to use of any time
09:43:36AM 3 points, such as 150 minutes, 180 minutes and 240 minutes to prove
09:43:41AM 4 immediate release.

09:43:43AM 5 THE COURT: I think they're not dispositive. It may be
09:43:48AM 6 that there's an inference to be drawn, that inference may well be
09:43:51AM 7 weak, but the Court is mindful of the, you know, roughly,
09:43:53AM 8 30-minute time for immediate release as the dispositive one as I
09:43:59AM 9 have construed the claim. So I don't think that makes it
09:44:01AM 10 inadmissible, but it certainly goes to the weight.

09:44:04AM 11 MR. RAKOCZY: Understood, Your Honor. We just wanted
09:44:05AM 12 to preserve that objection.

09:44:06AM 13 And then the last objection I had was Slide 73. And
09:44:10AM 14 this is just to renew our Daubert objection to testimony, any
09:44:16AM 15 testimony attempting to infer composition ratios from mean plasma
09:44:24AM 16 concentration data, which was the subject of our Daubert. Again,
09:44:26AM 17 I understand Your Honor denied it, but I just want to renew it
09:44:30AM 18 for the record.

09:44:31AM 19 THE COURT: Look, the ultimate test is whether they
09:44:33AM 20 infringe the terms of the patent. Mr. Flattmann's opening
09:44:39AM 21 statement went hard on things and, you know, the FDA and blood
09:44:44AM 22 levels and the like. That's not the governing legal test as to
09:44:50AM 23 whether they want to draw inferences from them. You know,
09:44:53AM 24 there's plenty of room to dispute how strong an inference I
09:44:58AM 25 should draw from them. I don't think it makes it inadmissible.

09:45:01AM 1 MR. RAKOCZY: Understood, Your Honor. Thank you.

09:45:02AM 2 THE COURT: All right. Please go ahead and swear the
09:45:05AM 3 witness.

09:45:05AM 4 EDWARD RUDNIC, called and sworn.

09:45:24AM 5 THE COURT: Good morning, Mr. Rudnic. She's the most
09:45:27AM 6 important person in the room. If she can't hear you, it doesn't
09:45:30AM 7 wind up on the record. So please be sure not shaking your head
09:45:34AM 8 or nodding your head. If at any time you can't hear anybody, let
09:45:38AM 9 us know.

09:45:39AM 10 If you want to take a break, we're going to take a
09:45:43AM 11 midmorning break sometime in the next hour, bathroom break,
09:45:47AM 12 anything else, that's absolutely fine. And I will let people in
09:45:51AM 13 the courtroom, by the way, I'm not bothered if some of you need
09:45:53AM 14 to slip out quietly and go to the restroom and come back. Just
09:45:53AM 15 do it unobtrusively.

09:45:59AM 16 But we'll take a break and let us know if there's a
09:46:02AM 17 time that either of you need to take it or it's a very logical
09:46:04AM 18 time to take it. Counsel may figure out a time before
09:46:08AM 19 transitioning to some other topic that makes sense to take a
09:46:12AM 20 break in half an hour or 45 minutes or whatever. And I will
09:46:17AM 21 defer to you and let you go.

09:46:19AM 22 MR. COCHRAN: Thank you, Your Honor.

09:46:21AM 23 THE WITNESS: Before we start, can I try the
09:46:26AM 24 microphone?

09:46:31AM 25 THE COURT: Yes.

09:46:31AM 1 DIRECT EXAMINATION

09:46:31AM 2 BY MR. COCHRAN:

09:46:33AM 3 Q. Good morning, Dr. Rudnic. Just for the record, please state
09:46:35AM 4 your full name.

09:46:36AM 5 A. Edward Michael Rudnic.

09:46:39AM 6 Q. How do you spell your last name?

09:46:43AM 7 A. R-U-D-N-I-C.

09:46:43AM 8 Q. I understand you will be using a demonstrative to assist you
09:46:46AM 9 in your testimony today; is that correct?

09:46:48AM 10 A. Yes, sir.

09:46:48AM 11 Q. Who prepared those?

09:46:49AM 12 A. I did with assistance of counsel.

09:46:53AM 13 Q. Where are you currently employed, Dr. Rudnic?

09:46:55AM 14 A. I am the chief operating officer and head of research and
09:46:58AM 15 development for Maxwell Biosciences in Austin, Texas.

09:47:05AM 16 Q. What does Maxwell Biosciences do as a business?

09:47:08AM 17 A. We discover and develop new chemical entities for
09:47:16AM 18 anti-infectives. Mostly antibacterials and antifungals at the
09:47:20AM 19 moment.

09:47:20AM 20 Q. Can you please describe your educational background,
09:47:23AM 21 starting with your undergraduate degree.

09:47:26AM 22 A. I have a Bachelor's of science in pharmacy, which allowed me
09:47:29AM 23 to become a registered pharmacist. I went on for a Master's of
09:47:34AM 24 Science in pharmaceuticals. And then a Ph.D. in pharmaceutical
09:47:39AM 25 sciences all from the University of Rhode Island.

09:47:42AM 1 Q. what year did you earn your PH.D?

09:47:43AM 2 A. 1982.

09:47:46AM 3 Q. Can you briefly describe your professional experience.

09:47:48AM 4 A. I started with about one-year onsite research internship at
09:47:54AM 5 Merck in Pennsylvania, while I was in graduate school, creating
09:47:58AM 6 research information for my Master's degree. I then, also, spent
09:48:06AM 7 about 8 months onsite at Pfizer in New York doing additional
09:48:11AM 8 research for my graduate degree.

09:48:14AM 9 Following graduation, my first full-time job was at
09:48:17AM 10 Bristol Myers Squibb where I was in charge of a controlled
09:48:21AM 11 release development laboratory. So modified release dosage forms
09:48:26AM 12 their evaluation, testing, and formulation. I then moved from
09:48:32AM 13 that position to be manager of pharmaceutical process development
09:48:41AM 14 at Merck where my job was to manage the scale of all non-sterile
09:48:48AM 15 dosage forms at the company.

09:48:49AM 16 So all tablets, capsules, ointments, creams,
09:48:53AM 17 suspensions, liquids, powders, stuff like that. Big job. And we
09:48:56AM 18 developed a lot of products at -- while I was there. I played a
09:49:03AM 19 major role in the development and ANDA filing of Claritin, a very
09:49:08AM 20 successful cold and allergy product that's still on the market
09:49:13AM 21 today. Cumulative sales of that product and product line are
09:49:17AM 22 about \$40 billion. So big deal.

09:49:21AM 23 I left that position when we had acquired Key
09:49:31AM 24 Pharmaceuticals in Miami, Florida. I was promoted to director of
09:49:34AM 25 formulation development. I went down to run the formulation and

development and scale-up activities down at what became known as Schering, Miami. I was responsible for those things for about 5 years. Left that position to become vice president and head of research for a small company called Pharmavene. And while I was at Pharmavene, I had invented three drug products; Adderall XR, Carbatrol and Equetro.

Those three products together caught the attention of Shire Pharmaceuticals, a British company who then acquired Pharmavene. I then became the head of US research for Shire. Preclinical research all the way through initial clinical studies, all the way through pivotal clinical study and post marketing studies. And that position I had all of the formulation development scale up and manufacturing at a pilot scale reporting to me. I had medical clinical regulatory affairs and basic research all reporting to me.

I had that position for about 3 years. When the chairman of Shire had convinced me to leave Shire, to start a new antibiotic company as the CEO, which they were funding through his venture fund. I started that company as Employee 1 and within 3 years took it public on the NASDAQ. It was the first S1 filing to go public post -- and was actually kind of an interesting ride on that IPO.

But it was an antibiotics company. I invented two antibiotics products there that ultimately won FDA approval. And I had left that company after 9 years as CEO and put it in the

09:51:48AM 1 hands of a marketing and sales team. I went on to do some
09:51:52AM 2 venture work and hedge fund work. Didn't particularly like that
09:51:56AM 3 much. I liked operational roles better. I came back to be the
09:52:00AM 4 chief operating officer, and ultimately CEO, of a publicly traded
09:52:07AM 5 Australian company called QRX, it's a pain company. They were in
09:52:11AM 6 under duress and I took over the company as CEO at the request of
09:52:15AM 7 their board to see if I could save it with the FDA. I couldn't.

09:52:19AM 8 So I left QRX and became the CEO of a pharmaceutical
09:52:26AM 9 technology company in Austin, Texas called Dispersol
09:52:31AM 10 Technologies. This is a company with fabulous unique technology
09:52:36AM 11 for the improvement of dissolution and absorption of hard to
09:52:41AM 12 absorb drugs. My role as CEO, and all over research company, was
09:52:48AM 13 to get the technology validated.

09:52:52AM 14 I was able to take two compounds, take it through Phase
09:52:57AM 15 1, Phase 2, and ultimately into Phase 3 clinical trials, where
09:53:01AM 16 they are today. The company has decided to out-license those
09:53:06AM 17 compounds and turn the company into more of a services model.
09:53:13AM 18 And I'm not much on sales and marketing. I decided to stick with
09:53:20AM 19 research and operations, so I moved over to Maxwell Biosciences
09:53:26AM 20 almost 2 years ago.

09:53:27AM 21 Q. Are you still doing research?

09:53:29AM 22 A. Every day.

09:53:31AM 23 Q. Do you also hold any academic positions?

09:53:34AM 24 A. I am the assistant associate -- no. Associate Professor of
09:53:42AM 25 Pharmaceuticals at the University of Maryland and associate

professor of Pharmaceutics at the University of Rhode Island.

Q. Have you published any scientific literature?

A. I have over 20 publications in peer review journals. And seven book chapters in standard reference textbooks, such as Remingtons and Modern Pharmaceutics.

Q. What is the general subject matter of those publications?

A. Starts with oral solid dosage forms, coating tablets, capsules, pellets, drug delivery, novel drug delivery systems, quality control scale up, it's polymer science. And quality control.

Q. When you say "polymer science," what do you mean?

A. Early in my career I did a fair amount of research on the impact of molecular structure variations of polymers and how that affected those polymers' ability to either enhance or suppress drug delivery in the body.

Q. Are you involved in any professional organizations related to pharmaceuticals?

A. Yes, I am a charter member of the American Association of Pharmaceutical Scientists. I have been very active in that organization since its founding. And I've been involved in various discussion groups, working groups and invited to lecture at the Arden House Conference, which is very prestigious thing.

I have also been an invited lecturer at various APS events, such as the Land O Lakes conferences and the national meetings.

09:55:34AM 1 Q. Any other professional organizations?

09:55:37AM 2 A. I am a fellow of the United States Pharmacopeial Convention
09:55:41AM 3 and I am also the past vice chair of biotechnology for the tech
09:55:48AM 4 counsel of Maryland. And the past chairman or chairman emeritus
09:55:52AM 5 of the tech counsel of Maryland.

09:55:55AM 6 Q. What does it mean to be a fellow of the USP?

09:55:58AM 7 A. It's a very prestigious thing. I wasn't aware of how
09:56:03AM 8 difficult it was to get it at the time, but they choose
09:56:06AM 9 relatively young researchers that have done a lot of very
09:56:10AM 10 important work on drug standards or material specifications. And
09:56:17AM 11 my work on polymers caught their attention and I was awarded a
09:56:21AM 12 fellowship.

09:56:21AM 13 Q. Thank you. And what does it mean to be the chairman of the
09:56:26AM 14 Tech Council of Maryland?

09:56:27AM 15 A. This is actually a very prestigious role. So the Tech
09:56:32AM 16 Council of Maryland is the largest traded association in that
09:56:34AM 17 state. It represents about 400,000 jobs in a state of 8 million
09:56:38AM 18 people. And it represents high technology companies, so think
09:56:45AM 19 Lockheed Martin, NASA and IBM and biotech companies. So think
09:56:54AM 20 AstraZeneca, Amgen and hundreds of small biotech companies and I
09:56:57AM 21 was elected by peer CEOs.

09:57:02AM 22 Q. Are you the name inventor on any patents?

09:57:06AM 23 A. Yes, I am the inventor or coinventor on 58 issued US
09:57:11AM 24 patents. I was recently informed that the patent office has
09:57:16AM 25 granted claims on number 59, so that should issue already -- paid

the issue fee, so should issue soon. So 58 going on 59 and there are 12 pending along with about 250 international patents and publications that are related to those 58.

Q. Thank you. Of the drugs you have worked on over your career, how many have you commercialized?

A. Over 80 products.

Q. Collectively, how much in cumulative sales of those 80 commercialized products earned?

A. Last time I checked was well over \$100 billion.

Q. And of those over 80 commercialized products, how many were you the lead inventor on?

A. Seven.

Q. Can you name them?

A. Adderall XR, Carbatrol, Equetro, UNI-DUR, Moxatag, GoodNight and GI Comfort.

Q. How common is for someone to be the lead inventor on seven commercialized drug products?

A. It's not common. I have worked with a lot of incredibly smart and dedicated people that have worked their entire careers and never had a drug product get on the market.

THE COURT: How much of those involved extended release. I'm guessing --

THE WITNESS: All of them, Your Honor. All of them.

BY MR. COCHRAN:

Q. So what challenges are there in commercializing drug

1 products containing delayed release components?

2 A. Quite a bit. As I mentioned, it's not uncommon to have
3 people work in this industry and never have a drug product get to
4 the market, because of toxicology issues or other things that
5 happened during the normal course of development. But when you
6 modify the release of compounds, more things can happen.

7 I've seen extended release, modified release dosage
8 forms cause toxicity that you didn't see before. I have seen
9 therapeutic failure that you didn't see before with an immediate
10 release. So added risk starts to come when you start to do those
11 things.

12 Q. Dr. Rudnic, do you have a witness book containing documents
13 that you intend to use today?

14 A. Yes.

15 Q. Let's turn to PTX-214. It's Tab Number 1.

16 Do you recognize this document?

17 A. Yes.

18 Q. What is it?

19 A. It is a reasonably recent version of my CV.

20 Q. Does your CV fairly and accurately summarize your education,
21 employment, publications and professional accomplishments?

22 A. Yes.

23 MR. COCHRAN: Your Honor, Plaintiffs would like to
24 offer PTX-214 into evidence.

25 THE COURT: Any objection?

10:00:05AM 1 MR. RAKOCZY: No objection.

10:00:07AM 2 THE COURT: So entered.

10:00:07AM 3 (Exhibit Number PTX-214 was admitted.)

10:00:10AM 4 MR. COCHRAN: We would also like to offer Dr. Rudnic as
10:00:13AM 5 an expert in invention, design, development, testing,
10:00:14AM 6 manufacturing and commercialization of drug products, including
10:00:18AM 7 pharmaceutical formulation.

10:00:20AM 8 THE COURT: Any objection or request for voir dire?

10:00:23AM 9 MR. RAKOCZY: Subject to the grounds stated in our
10:00:29AM 10 Daubert motion, which we understand Your Honor denied, we have
10:00:29AM 11 no objection.

10:00:34AM 12 THE COURT: You may proceed.

10:00:34AM 13 BY MR. COCHRAN:

10:00:35AM 14 Q. Can you provide a high-level summary of the issues in this
10:00:39AM 15 case?

10:00:39AM 16 A. Yes. My opinions can be pretty much summarized into two
10:00:47AM 17 statements. One is that the asserted patent claims cover a
10:00:51AM 18 modified release formulation of doxycycline, which contains a
10:00:55AM 19 30-milligram immediate release portion and a 10-milligram delayed
10:00:58AM 20 release portion. And Lupin's non-infringement defense rises and
10:01:04AM 21 falls with the amount of immediate release and delayed release
10:01:07AM 22 doxycycline it alleges in its formulation.

10:01:10AM 23 Q. Can you walk us through some of the concepts that you plan
10:01:13AM 24 to speak about today?

10:01:15AM 25 A. Sure. So first I'm going to talk about the scientific

1 background and there's -- it's important to talk about a variety
2 of things. The most important things to talk about in vitro
3 dissolution testing and its limitations. There are limitations
4 to in vitro testing.

5 So every test, every set of data tells you something,
6 but it's important to understand what it doesn't tell you. It's
7 important to understand what its limitations are and I am going
8 to talk about that.

9 In addition, doxycycline has a very pronounced
10 absorption window. It's been well documented over the last 30
11 years and it's been well documented in the Oracea NDA, so this is
12 something that's been discussed at virtually every case for
13 doxycycline since 2011.

14 I'm going to talk about the product overview, what
15 Oracea and Lupin labels tell us about each product. And again,
16 as Mr. Flattmann outlined at the beginning, the only real dispute
17 is the quantities of IR and DR. In terms of infringement, what
18 I'm going to talk about is Lupin's design and how it functions,
19 renders it to be a 30-milligram IR and 10-milligram DR and as a
20 result, it infringes the asserted claims.

21 Q. Thank you, Dr. Rudnic.

22 Let's talk about the scientific background a bit,
23 starting with in vitro dissolution. How does the USP website
24 define in vitro dissolution testing?

25 A. They say that a dissolution experiment evaluates the rate

1 and extent that a compound forms a solution under carefully
2 controlled conditions.

3 Q. Thank you. Can you please turn to PTX-143 in your witness
4 book. This is Tab 2.

5 A. Yes.

6 Q. Do you recognize this document?

7 A. Yes.

8 Q. What is it?

9 A. It is an excerpt from the USP website talking about
10 dissolution test.

11 Q. Did you consider PTX-143 in forming your opinions in this
12 case?

13 A. Yes.

14 THE COURT: Remind me what USP is.

15 THE WITNESS: United States Pharmacopeia for drugs and
16 materials used in pharmaceutical products.

17 MR. COCHRAN: Plaintiffs would like to offer PTX-143
18 into evidence.

19 THE COURT: Any objection?

20 MR. RAKOCZY: No objection.

21 THE COURT: So admitted.

22 (Exhibit Number PTX-143 was admitted.)

23 BY MR. COCHRAN:

24 Q. Dr. Rudnic, what information is in vitro dissolution testing
25 designed to provide?

1 A. well, it is used to assess the lot-to-lot quality of drug
2 products. It guides development of new formulation and ensures
3 continuing product quality and performance after certain changes.

4 Q. Can you please turn to PTX-163. This is tab 3.

5 A. Yes.

6 Q. Do you recognize this document?

7 A. Yes, this is the FDA guidance for industry on dissolution
8 testing of immediate release solid oral dosage forms.

9 Q. And is this the FDA guidance you're referencing on your
10 slide?

11 A. Yes.

12 MR. COCHRAN: Your Honor, I would like to offer PTX-163
13 into evidence.

14 THE COURT: Any objection?

15 MR. RAKOCZY: No objection, Your Honor.

16 THE COURT: Admitted.

17 (Exhibit Number PTX-163 was admitted.)

18 BY MR. COCHRAN:

19 Q. Dr. Rudnic, what are the limitations of in vitro dissolution
20 testing?

21 A. It's important, especially for the purpose of this case to
22 note that their primary purpose is quality control. The Lupin
23 experts continually try to point to the fact that certain times
24 of release in dissolution testing are one-to-one relationships
25 what happens in the body. That is not true. In fact, the FDA

1 and the USP are very clear their discussions about their test
2 that that is not the case.

3 So it's important to understand that what these in
4 vi tro release tests are meant to be, they're quality control
5 tests. I've said this consistently throughout this case. Now
6 failure of these tests is a concern. But one to one being able
7 to tell exactly what is released in the body based on these tests
8 is not true. The apparatus design is not the same as what
9 happens in the human body. The human stomach is, roughly, got
10 about 250 MLs of gastric fluid in it.

11 Q. What do you mean by MLs?

12 THE COURT: Quarter of a liter. I understood. Go on.

13 THE WITNESS: Yes, sir.

14 So the testing vessel holds about 900 MLs, almost one
15 liter. So in addition you have a paddle that stirs very slowly
16 at one revolution per minute, roughly. And the agitation in the
17 stomach is a whole lot different.

18 The other thing is that the media for a lot of these pH
19 1.1 that doesn't exist in your stomach, it is meant to be the
20 fluid that your stomach actually exudes, but the pH of the
21 stomach, if it were 1.1 you wouldn't have much of a stomach
22 left after a while, you would have a lot of holes in it. So our
23 Mother Nature has given us buffers and salts and other things
24 that help protect the lining of our stomach from that gastric
25 fluid, and such, the pH is higher. Typically about 2.2 at the

10:07:10AM 1 lowest to about 5 at the highest.

10:07:14AM 2 And I've been very consistent saying that if you want
10:07:16AM 3 to pick a good average pH for the stomach, 3 is the number. But
10:07:23AM 4 what we're going to show is that the pH of time of drug
10:07:26AM 5 administration is a bit higher.

10:07:26AM 6 BY MR. COCHRAN:

10:07:29AM 7 Q. So in your opinion, Dr. Rudnic, can a person of ordinary
10:07:33AM 8 skill in the art rely exclusively on in vitro dissolution
10:07:38AM 9 testing?

10:07:38AM 10 A. No. In fact, if you could the FDA wouldn't require
10:07:41AM 11 bioequivalence testing.

10:07:44AM 12 Q. Let's turn to PTX-137 of your witness book. This is tab 4.

10:07:48AM 13 A. Yes, I got it.

10:07:50AM 14 Q. What is this document?

10:07:51AM 15 A. This is also from the FDA website on dissolution methods and
10:08:00AM 16 disclaimer.

10:08:01AM 17 Q. And did you rely on PTX-137 in forming your opinions in this
10:08:07AM 18 case?

10:08:07AM 19 A. Yes.

10:08:08AM 20 MR. COCHRAN: Your Honor, Plaintiffs would like to
10:08:09AM 21 offer PTX-137.

10:08:11AM 22 THE COURT: Any objection?

10:08:12AM 23 MR. RAKOCZY: No objection, Your Honor.

10:08:13AM 24 THE COURT: Admitted.

10:08:13AM 25 (Exhibit Number PTX-137 was admitted.)

10:08:13AM 1 BY MR. COCHRAN:

10:08:14AM 2 Q. Let's also turn to PTX-145. That's tab 5.

10:08:14AM 3 A. Got it.

10:08:21AM 4 Q. What is this document?

10:08:21AM 5 A. This is a paper by Deanna Mudie, Gordon Amidon, and Greg
10:08:29AM 6 Amidon from the University of Michigan, they're probably happy
10:08:34AM 7 this morning.

10:08:36AM 8 Gordan Amidon is one of the best experts in terms of
10:08:40AM 9 dissolution testing and what it means for evaluation in vivo and
10:08:44AM 10 in this paper they outline limitations to in vitro testing and
10:08:52AM 11 correlation to in vivo activity and performance.

10:08:56AM 12 Q. Did you rely on this Mudie article in your testimony?

10:08:59AM 13 A. Yes.

10:09:01AM 14 Q. Did you consider --

10:09:03AM 15 MR. COCHRAN: Your Honor, Plaintiffs would like to
10:09:04AM 16 offer PTX-145 into evidence.

10:09:07AM 17 THE COURT: Any objection?

10:09:08AM 18 MR. RAKOCZY: No objection, Your Honor.

10:09:09AM 19 THE COURT: Admitted.

10:09:09AM 20 (Exhibit Number PTX-145 was admitted.)

10:09:09AM 21 BY MR. COCHRAN:

10:09:12AM 22 Q. Now Dr. Rudnic, is there an industry standard for basic drug
10:09:18AM 23 release or testing basic drug release?

10:09:22AM 24 A. Well, I would say no one standard, but probably the majority
10:09:29AM 25 of immediate release dosage forms are tested at pH 1.1. As I

10:09:34AM 1 pointed out, this is kind of the worst case pH that you can have.
10:09:40AM 2 This is the same pH of the acid that your stomach excretes but
10:09:45AM 3 not the pH that is in the stomach in general. So for IR
10:09:50AM 4 products, this is probably the majority of testing.

10:09:55AM 5 Q. would you consider pH 1.1 a bio relevant pH?

10:09:59AM 6 A. No, because it doesn't exist in the stomach as a general pH.
10:10:05AM 7 It is meant as a QC test. The other thing is it typically runs
10:10:10AM 8 for at least 2 hours. GI transit is certainly about an hour or
10:10:14AM 9 less.

10:10:15AM 10 Q. why would Lupin use pH 1. --

10:10:18AM 11 THE COURT: GI transits over what part of the
10:10:22AM 12 gastrointestinal tract are you talking about --

10:10:22AM 13 THE WITNESS: Sorry, Your Honor.

10:10:22AM 14 THE COURT: From where to -

10:10:26AM 15 THE WITNESS: Gastric. So you start with the stomach
10:10:29AM 16 and the transit is somewhat less than an hour to go through the
10:10:34AM 17 pylorus into the intestinal tract.

10:10:37AM 18 THE COURT: From entering the stomach to --

10:10:39AM 19 THE WITNESS: From swallowing.

10:10:39AM 20 THE COURT: From swallowing.

10:10:40AM 21 THE WITNESS: From the time it leaves your stomach to
10:10:42AM 22 go into the small intestine.

10:10:47AM 23 THE COURT: Okay. The duodenum?

10:10:47AM 24 THE WITNESS: Duodenum, yes.

10:10:49AM 25 THE COURT: Got it. Mouth, duodenum, one hour?

10:10:51AM 1 THE WITNESS: Correct.

10:10:53AM 2 Now you then go into the duodenum and then at some
10:10:58AM 3 point, and this varies considerably depending on a lot of
10:11:03AM 4 factors, you then go into the duodenum and then ilium and
10:11:09AM 5 ultimately the colon and then it's out.

10:11:09AM 6 BY MR. COCHRAN:

10:11:13AM 7 Q. So Dr. Rudnic, why would Lupin use pH 1.1 in their in vitro
10:11:20AM 8 dissolution testing?

10:11:21AM 9 A. This is pretty much what the FDA asks you to do for
10:11:23AM 10 immediate release dosage forms. Also when they do a modified
10:11:30AM 11 release dosage form they want you to do a mixed test where you
10:11:35AM 12 start with pH 1.1, again, a worst case for 2 hours. And then
10:11:40AM 13 they recommend that you then test for 4.5 -- at pH 4.5 and all
10:11:47AM 14 the way up to about pH 7.5.

10:11:50AM 15 Q. Why would they do that?

10:11:51AM 16 A. Because they recognize that a lot of controlled release
10:11:55AM 17 dosage forms have a full day of drug in them and so they are
10:12:03AM 18 trying to look for dose dumping, which is a concern. So you
10:12:07AM 19 don't want to have a big spike of a full day's dose of drug. So
10:12:11AM 20 that's the purpose for testing at pH 1.1 for 2 hours, make sure
10:12:15AM 21 you don't have that dose dumping. And that whatever controlling
10:12:20AM 22 mechanism you have is robust enough to get through the stomach.

10:12:25AM 23 In addition, you then -- the FDA then asks you to test
10:12:30AM 24 at pHs of 4.5 all the way to 7.5. This is all through FDA
10:12:37AM 25 guidances that have been around for over 20 years.

10:12:42AM 1 Q. Dr. Rudnic, if you wanted to test a product at a pH of the
10:12:46AM 2 stomach, what pH values might you use?

10:12:51AM 3 A. I think you take a look at pHs at the extremes, probably
10:12:55AM 4 start at 1.1 and look at the other extreme 4.5, 5. And some pH
10:13:05AM 5 in between, but certainly those extremes.

10:13:08AM 6 Q. Let's turn to PTX-149 in your witness book. This is tab 6.

10:13:08AM 7 A. Yes.

10:13:14AM 8 Q. What is this document?

10:13:15AM 9 A. This is a paper by Lida Kalantzi. She was a researcher in
10:13:22AM 10 Christos Reppas' group in Greece.

10:13:23AM 11 Q. Did you consider PTX-149 in forming your opinions in this
10:13:28AM 12 case?

10:13:28AM 13 A. Yes, I did.

10:13:29AM 14 MR. COCHRAN: Your Honor, Plaintiffs would like to
10:13:30AM 15 offer PTX-149 into evidence.

10:13:32AM 16 THE COURT: As I understand it, Kalantzi is agreed
10:13:35AM 17 upon; correct? And Schneider, that was the subject of the
10:13:37AM 18 objection; right?

10:13:38AM 19 MR. RAKOCZY: Correct, Your Honor. No objection to
10:13:40AM 20 Kalantzi.

10:13:41AM 21 THE COURT: Admitted.

10:13:41AM 22 (Exhibit Number PTX-149 was admitted.)

10:13:41AM 23 BY MR. COCHRAN:

10:13:44AM 24 Q. Dr. Rudnic, what does the Kalantzi article tell you?

10:13:48AM 25 A. First let's talk about what Kalantzi did. FDA requires that

10:13:55AM 1 when you test a drug product that you take 240 ML of water and
10:14:01AM 2 you take whatever test product you are going to test with that.
10:14:06AM 3 And so Kalantzi tested what actually would be the pH in the
10:14:10AM 4 stomach given the FDA testing parameters.

10:14:15AM 5 And so here, what they showed -- and unfortunately a
10:14:19AM 6 bunch of unfortunate graduate students participated in this trial
10:14:22AM 7 and they aspirated out gastric contents at 20 minutes, 40 minutes
10:14:27AM 8 and 60 minutes. I'm glad I wasn't the grad student in that
10:14:27AM 9 study.

10:14:35AM 10 But what they showed is that at 20 minutes was the
10:14:38AM 11 first time they were able to put a tube down and take samples
10:14:41AM 12 out, is that you can see the pH range is pretty wide and this
10:14:47AM 13 makes sense because you start with 250 ML of gastric fluid at,
10:14:53AM 14 roughly, pH 2 to 2.2, 2.3, and then you add about an equivalent
10:15:00AM 15 volume of water, which is typically 7. All right

10:15:04AM 16 So what's halfway between 2 and 7; 4 and a half. So it
10:15:09AM 17 makes a lot of sense you're going to get there. So what she
10:15:11AM 18 showed is that yeah, about the 75th percentile was right around 4
10:15:16AM 19 and a half. And you can see that if you were to do some sort of
10:15:22AM 20 a regression looking backwards towards the Y axis, you'd be up
10:15:29AM 21 around that 4 and a half. So -- and there are other -- other
10:15:36AM 22 people that have reproduced this.

10:15:39AM 23 Q. Dr. Rudnic, before we move on to the next slide, at your
10:15:42AM 24 deposition you were asked if you found any other article that
10:15:45AM 25 corroborated Kalantzi. Do you recall that?

10:15:48AM 1 A. Yes.

10:15:48AM 2 Q. And did you find one?

10:15:50AM 3 A. Yes.

10:15:57AM 4 Q. Let's go to Slide 14, please.

10:16:03AM 5 Dr. Rudnic, what conditions did Lupin use in its
10:16:08AM 6 bioequivalence studies?

10:16:10AM 7 A. Well, they did exactly what the FDA required them to do,
10:16:13AM 8 which is they had to administer 240 MLs of water to the subject,
10:16:19AM 9 when they took either Oracea or their ANDA product and -- before
10:16:24AM 10 they started testing. So time zero they took 240 MLs of water
10:16:30AM 11 and whatever test product they were about to start testing.

10:16:35AM 12 Q. Now, why is that important?

10:16:37AM 13 A. Because a person of skill in the art would know that pH 4.5
10:16:41AM 14 is physiologically relevant stomach pH and subjects would have a
10:16:48AM 15 median pH of 4.5 upon drug administration immediately.

10:16:52AM 16 Q. Let's all turn to PTX-191 in your witness book, Dr. Rudnic.
10:16:59AM 17 This is tab 8.

10:16:59AM 18 A. Yes.

10:17:00AM 19 Q. Do you recognize this document?

10:17:02AM 20 A. Yes.

10:17:03AM 21 Q. Can you tell us what it is?

10:17:04AM 22 A. This is the report synopsis for the Lupin bioequivalence
10:17:08AM 23 study, that we were just talking about.

10:17:12AM 24 Q. Did you consider PTX-191 in forming your opinions in this
10:17:14AM 25 case?

10:17:14AM 1 A. Yes.

10:17:16AM 2 MR. COCHRAN: Your Honor, Plaintiffs would like to
10:17:17AM 3 offer PTX-191 into evidence.

10:17:19AM 4 THE COURT: Objection?

10:17:20AM 5 MR. RAKOCZY: Subject to our Daubert motion, Your
10:17:20AM 6 Honor, no objection.

10:17:24AM 7 (Exhibit Number PTX-191 was admitted.)

10:17:24AM 8 THE COURT: You developed seven drugs. Did you test
10:17:27AM 9 each and every one of them at 4.5 pH?

10:17:30AM 10 THE WITNESS: Yes, sir. Yes, Your Honor.

10:17:32AM 11 THE COURT: As part of the approval process?

10:17:36AM 12 THE WITNESS: Many times, yes. Yes, Your Honor.

10:17:36AM 13 BY MR. COCHRAN:

10:17:39AM 14 Q. Dr. Rudnic, let's move on to another topic of scientific
10:17:43AM 15 background. What is an absorption window?

10:17:47AM 16 A. So drugs in order to get into the bloodstream have to be
10:17:52AM 17 absorbed. If they are absorbed at a certain part of your
10:17:57AM 18 intestinal tract, at a very high degree, but yet before that area
10:18:06AM 19 and after that area, you find a decrease, significant decrease in
10:18:11AM 20 absorption. The area of high absorption is considered to be
10:18:16AM 21 called an absorption window. All right. So these occur for many
10:18:22AM 22 drugs. There are some drugs where they don't occur, but for
10:18:26AM 23 doxycycline, yes.

10:18:27AM 24 Q. So doxycycline has an absorption window?

10:18:29AM 25 A. It sure does.

10:18:31AM 1 Q. How do you know?

10:18:32AM 2 A. Well, first of all, in every single case that I have done
10:18:36AM 3 with Oracea over the years, the opposing side has thrown at us
10:18:41AM 4 dozens of articles or book chapters talking about how there is an
10:18:47AM 5 absorption window for doxycycline. And in fact, most of these
10:18:51AM 6 articles talk about in generalities about how it's in the upper
10:18:55AM 7 part of the GI tract and there's one in particular that talks
10:18:58AM 8 about it being in the duodenum.

10:19:00AM 9 THE COURT: Just a moment. Let's go over some basic
10:19:04AM 10 physiology here. So the gastric is the adjective for stomach.
10:19:09AM 11 The pylorus is the exit from the stomach into the duodenum?

10:19:12AM 12 THE WITNESS: Yes.

10:19:13AM 13 THE COURT: The duodenum is the beginning of the small
10:19:15AM 14 intestine?

10:19:15AM 15 THE WITNESS: Yes.

10:19:16AM 16 THE COURT: What are the parts that you count as the
10:19:19AM 17 distal small intestine?

10:19:21AM 18 THE WITNESS: The Jejunum and the ileum. So it goes,
10:19:23AM 19 Your Honor, the stomach is not an absorptive organ.

10:19:23AM 20 THE COURT: Okay.

10:19:29AM 21 THE WITNESS: The purpose of the stomach is to take
10:19:33AM 22 acid and enzymes and break down proteins into amino acids so that
10:19:41AM 23 your body can then absorb them in your intestinal tract. And
10:19:44AM 24 then you can reassemble them into proteins that your body then
10:19:48AM 25 needs.

10:19:49AM 1 THE COURT: So the entirety of the small intestine
10:19:54AM 2 compromise of the duodenum, the jejunum and ilium?

10:19:58AM 3 THE WITNESS: Yes. And then you go to the large
10:19:59AM 4 intestine and the colon.

10:20:01AM 5 THE COURT: Colon is a synonym for the entire large
10:20:05AM 6 intestine?

10:20:06AM 7 THE WITNESS: Correct. Gastroenterologists might have
10:20:13AM 8 slight issue with me there, but not much.

10:20:14AM 9 BY MR. COCHRAN:

10:20:14AM 10 Q. What else can you tell us about doxycycline absorption
10:20:17AM 11 window?

10:20:18AM 12 A. Well, in general this absorption window was known, but we
10:20:24AM 13 didn't know how much of an absorption window there was until the
10:20:28AM 14 folks that developed Oracea did what's called scintigraphic
10:20:33AM 15 study. And I've done about 12 scintigraphic studies in my
10:20:38AM 16 career.

10:20:38AM 17 These are really specified high level and very
10:20:41AM 18 expensive studies. What you do is you radio label the drug and
10:20:47AM 19 you then can follow it using gamma scintigraphy as to where the
10:20:53AM 20 drug is being absorbed in regions of the GI tract. And for the
10:20:57AM 21 first time, the folks at -- who developed Oracea, show that all
10:21:01AM 22 the literature in animal studies earlier was correct. Most of
10:21:07AM 23 the absorption does, indeed, occur in the early small intestine
10:21:11AM 24 in the duodenum.

10:21:12AM 25 But when you go to the jejunum and the ilium, you drop

10:21:16AM 1 to less than half. And then you go to the colon and you're below
10:21:21AM 2 5 percent. So this is a fairly, I would call, pronounced
10:21:27AM 3 absorption window.

10:21:27AM 4 BY MR. COCHRAN:

10:21:29AM 5 Q. So let's go to PTX-176 in your witness book. This is tab 9.

10:21:29AM 6 A. Yes.

10:21:36AM 7 Q. Do you recognize this document?

10:21:37AM 8 A. Yes.

10:21:39AM 9 Q. Is this the Scintipharma study you were just referring to?

10:21:43AM 10 A. Yes.

10:21:43AM 11 MR. COCHRAN: Your Honor, Plaintiffs would like to
10:21:44AM 12 offer PTX-176 into evidence.

10:21:49AM 13 MR. RAKOCZY: No objection, Your Honor.

10:21:50AM 14 THE COURT: Admitted.

10:21:50AM 15 (Exhibit Number PTX-176 was admitted.)

10:21:50AM 16 BY MR. COCHRAN:

10:21:53AM 17 Q. Dr. Rudnic, how is doxycycline absorption's window relevant
10:21:57AM 18 in this case?

10:21:58AM 19 A. Well, it's important to put this in the context of the Chang
10:22:04AM 20 patents. So the objective of Chang was to achieve a steady state
10:22:13AM 21 blood level high enough to be effective to have a beneficial
10:22:17AM 22 effect on the treatment of rosacea, which is reddening of the
10:22:21AM 23 skin. It's a type of acne. But not high enough to exert an
10:22:25AM 24 antibacterial effect. So at 0.1 micrograms per mL, it's been
10:22:31AM 25 well shown that you start to have an antiinflammatory effect

10:22:35AM 1 which calms down the redness in the face for rosacea.

10:22:42AM 2 However, at 1.0 micrograms per mL, right around there,
10:22:44AM 3 you start to get antibiotic effect. Now remember, this is a
10:22:48AM 4 product you'll probably take for the rest of your life, as long
10:22:52AM 5 as you have rosacea. And if you were take an antibiotic every
10:22:55AM 6 day, you would ultimately develop a superinfection in your gut
10:22:59AM 7 and that is a life threatening condition.

10:23:01AM 8 THE COURT: This will not kill off gut flora. This
10:23:04AM 9 will not lead to resistant superbugs or anything like that?

10:23:07AM 10 THE WITNESS: Correct. So as long as you stay within
10:23:09AM 11 that range. And this is -- this is what the folks that developed
10:23:16AM 12 Oracea found, is that that can only be achieved with a very
10:23:20AM 13 specific ratio of 30:10 IR/DR. In fact, too much DR will
10:23:28AM 14 overshoot that absorption window and you will have lower
10:23:31AM 15 bioavailability. If you have too much IR, you'll peek too soon
10:23:36AM 16 and you won't last as long and maintain that antiinflammatory
10:23:42AM 17 effect for 24 hours.

10:23:43AM 18 So this is an absorption window that's very tight for a
10:23:46AM 19 drug that has to have a very narrow window or you're going to
10:23:49AM 20 start creating an antibiotic effect, you're going to create
10:23:52AM 21 resistant bacteria, a superinfection, all sorts of bad stuff.
10:23:57AM 22 All right? So important that you maintain it within this level,
10:24:00AM 23 but also you're dealing with a drug that is very, very pronounced
10:24:05AM 24 absorption window. You have to be very, very precise.
10:24:05AM 25

1 BY MR. COCHRAN:

2 Q. What else might happen if you have too much immediate
3 release doxycycline?

4 A. Well, again, you would have the concern of antibiotic effect
5 because you probably would breach that 1.0 micrograms per mL. In
6 fact, when they did some in silico modeling, the facts that
7 developed Oracea showed that.

8 Q. Let's move on to another topic. What is your definition of
9 a person of ordinary skill in the art?

10 A. Well a POSA or a person of ordinary skill in the art is a
11 person with education and experience in drug delivery and
12 formulation science as it relates to what we are talking about
13 here. And that person could be any person with a Bachelor's
14 degree with many years of experience or somebody with a higher
15 degree with lesser years of experience. And obviously, the kind
16 of experience matters, so relevant work experience.

17 Q. And what, if anything, did you rely on when forming your
18 definition of a POSA?

19 A. My 40 years of working shoulder to shoulder with men and
20 woman that have various educational degrees in various
21 disciplines of pharmaceutical development and I think this one
22 works just fine.

23 Q. And did you rely on this definition in forming your opinions
24 in this case?

25 A. I did.

1 Q. And Dr. Rudnic, what are those opinions?

2 A. Well, the opinions can be boiled down to one statement is
3 that Lupin's ANDA product infringes the Chang patents literally
4 and under the doctrine of equivalents. And by the Chang patents,
5 I mean US 8206740 and 7749532, what I call the Chang 740 and
6 Chang 532 patents.

7 Q. And what have you relied on in forming your infringement
8 opinions in this case?

9 A. Well, obviously the Chang patents. The Oracea NDA. Other
10 documents associated with their ANDA. The Lupin ANDA, documents
11 associated with their ANDA, documents provided by Lupin.
12 Literature. FDA guidances. USP standards and Court's Claim
13 Constructions of the terms that are in the Chang patents.

14 Q. And have you considered the opinions of Ms. Vivian Gray and
15 Dr. Graham Buckton on infringement?

16 A. Yes.

17 Q. Do you agree with those opinions?

18 A. On infringement, generally, no.

19 Q. Let's go to PTX-001 as well as 002. These are tabs 10 and
20 11 of the witness book.

21 A. Yes.

22 Q. Do you recognize these documents?

23 A. Yes.

24 Q. What are they?

25 A. This is the Chang 532 patent and the Chang 740 patent.

1 Q. And have you reviewed these patents in forming your opinions
2 in this case?

3 A. Yes.

4 MR. COCHRAN: Your Honor, Plaintiffs would like to
5 offer PTX-001 and 002 into evidence.

6 THE COURT: I take it there's no objection?

7 MR. RAKOCZY: No objection.

8 THE COURT: Admitted.

9 (Exhibit Numbers PTX-001 and PTX-002 were admitted.)

10 BY MR. COCHRAN:

11 Q. What claims of the Chang patents are being asserted against
12 Lupin?

13 A. In the Chang 740 patent claims, 1 and 20 are being asserted
14 and in the Chang 532 patent claims, 1 and 16 are being asserted.

15 Q. Walk us through Claim 1 of the 740 patent, please.

16 A. Sure. In Claim 1 of the 740 patent it starts out as an oral
17 pharmaceutical composition of doxycycline.

18 Q. What's the next limitation?

19 A. Says, once daily dosage that will give a steady state blood
20 levels of doxycycline of a minimum of .1 micrograms per mL and a
21 maximum of 1.0 micrograms per mL.

22 Q. How about the next one?

23 A. This is the composition consisting of immediate release or
24 IR portion comprising of 30 milligrams of doxycycline.

25 Q. And the next?

1 A. Delayed release or DR portion comprising 10 milligrams of
2 doxycycline.

3 Q. And the last?

4 A. And one or more pharmaceutical acceptable excipients.

5 Q. Let's turn to your next slide. What have you shown here?

6 A. Well, this contrasts the Claim 1 of both the 740 patent and
7 the 532 patent. And they're really quite similar, but what you
8 see in the Chang 532 patent is the word "about" appears before 30
9 milligrams doxycycline. And also that word "about" appears
10 before 10 milligrams of doxycycline, referring to both the IR and
11 DR components.

12 And then there's also a phrase that appears in the 532
13 patent in which the DR portion is in the form of pellets coated
14 with at least one enteric polymer.

15 Q. Let's go to your next slide. What have you shown here?

16 A. These are claim 19 of the Chang 740 patent and claim 15 of
17 the Chang 532 patent. And what you see here are method claims.
18 And so these are for treating rosacea in a mammal and you see
19 that claim 20 of the Chang 740 patent is a dependent claim says
20 that mammal is a human. And claim 15 of the Chang 532 patent,
21 similarly talks about treating rosacea in a mammal and the next
22 dependent claim talks about that being a human.

23 Q. Dr. Rudnic, how do the composition elements of these method
24 of treatment claims relate to the composition elements we just
25 discussed?

10:29:45AM 1 A. They're identical, with the exception of, you know, the 532
10:29:49AM 2 patent is slightly different than the 740 patent, but Claim 1 of
10:29:53AM 3 each of those patents is very, very similar to what you see in
10:29:59AM 4 these method claims.

10:30:00AM 5 Q. Thank you for that. And why have you decided to focus on
10:30:02AM 6 method of treatment claims?

10:30:04AM 7 A. Well, if you look at Court's Claim Construction of these
10:30:07AM 8 terms, both immediate release and portion construed to be
10:30:11AM 9 functional limitations, but the claim construction of immediate
10:30:14AM 10 release requires consideration of physiological conditions as
10:30:18AM 11 we'll see in a minute.

10:30:19AM 12 Q. Let's talk about those Claim Constructions. Next slide.
10:30:22AM 13 what have you shown here?

10:30:23AM 14 A. This is the Claim 1 of 740 patent where the word "immediate
10:30:28AM 15 release" and IR has been construed by this Court to be the
10:30:35AM 16 release that alters the subject steady state blood level of
10:30:39AM 17 doxycycline.

10:30:40AM 18 Q. Did you rely on this definition of immediate release in
10:30:43AM 19 forming your opinions in this litigation?

10:30:45AM 20 A. Yes.

10:30:46AM 21 Q. Let's go to your next slide. what have you shown here?

10:30:51AM 22 A. This is Claim 1 of 740 patent again where we talk about
10:30:55AM 23 delayed release. And I rely on the Sun Court's construction
10:30:59AM 24 where the release of a drug at a time other than immediately
10:31:02AM 25 following oral administration.

1 Q. And did you rely on this definition of delayed release in
2 this case?

3 A. Yes.

4 Q. Let's go to PTX-160, Tab 12 in your witness book.

5 A. Yes.

6 Q. Is this the Court's Claim Construction opinion in the Sun
7 litigation that you were referring to?

8 A. Yes.

9 MR. COCHRAN: Your Honor, Plaintiffs would like to
10 offer PTX-160 into evidence.

11 THE COURT: Any objection?

12 MR. RAKOCZY: One moment, Your Honor.

13 THE COURT: This is Judge Stark's opinion.

14 MR. RAKOCZY: I think it's odd to admit a Court
15 decision.

16 THE COURT: It's odd to admit opinions as evidence. I
17 mean, there's no objection you can consider it but I don't think
18 it's technically evidence, but you may refer to it as governing
19 law.

20 MR. RAKOCZY: Fair enough, Your Honor.

21 MR. COCHRAN: Thank you, Your Honor.

22 BY MR. COCHRAN:

23 Q. Let's turn to the next slide. What's your understanding of
24 the portion term?

25 A. So this is -- the portion is a term that appears after

1 immediate release IR and after delayed release DR. And the Sun
2 Court construed portion to mean any part of the claim composition
3 that releases drug immediately upon administration. And delayed
4 release to mean a part of the claim composition that delays
5 release of drug until a time other than immediately following
6 oral administration.

7 Q. And did you rely on these definitions of portion in this
8 case?

9 A. Yes.

10 Q. And what did you rely on for coming up with these Claim
11 Constructions?

12 A. The Court's Claim Construction.

13 Q. I was going to enter the Sun Court's post trial opinion,
14 Your Honor. We don't necessarily need to.

15 THE COURT: I don't think it needs to be admitted into
16 evidence, but I presume counsel have no objection to his
17 referring to it and using it in his discussion. Just not
18 technically evidence.

19 MR. RAKOCZY: No objection, Your Honor.

20 BY MR. COCHRAN:

21 Q. Let's go to your next slide. What's the definition of
22 "about"?

23 A. About appears in the Chang 532 patent, as I mentioned
24 earlier, and the Sun Court previously addressed the meaning of
25 that claim term about. And also in that same opinion, Judge

1 Stark noted that a POSA would understand that about 30 milligrams
2 represents a range of 27 to 33 milligrams of doxycycline. In
3 other words, a 10 percent variation or at most a range of 27 to
4 33 milligrams.

5 Q. So let's go to your next slide. What do these Claim
6 Constructions mean to you?

7 A. The claim terms have been construed to have functional
8 limitations, so how do these things function? So physiological
9 conditions are relevant to the infringement inquiry.

10 Q. Have you formed an opinion regarding whether Oracea is
11 covered by the asserted claims of the Chang patents?

12 A. Yes, I believe Oracea is a commercial embodiment of the
13 Chang patents.

14 Q. What did you base your opinion on?

15 A. Well, Galderma holds a new drug application 50-805, Oracea
16 capsules, which was approved by FDA on May 26 of 2006. And the
17 prescribing label, which part of that ANDA shows that Oracea
18 meets each and every limitation of the asserted claims.

19 Q. Let's go to PTX-162 in your witness book. This is tab 14.

20 A. Got it.

21 Q. Do you recognize this document?

22 A. Yes.

23 Q. What is it?

24 A. This is the Oracea label from their ANDA.

25 Q. Did you consider PTX-162 in forming your opinions in this

10:34:49AM 1 case?

10:34:49AM 2 A. Yes.

10:34:50AM 3 MR. COCHRAN: Your Honor, Plaintiffs would like to
10:34:51AM 4 offer PTX-162 into evidence.

10:34:53AM 5 THE COURT: Any objection?

10:34:54AM 6 MR. RAKOCZY: No objection, Your Honor.

10:34:55AM 7 THE COURT: Admitted.

10:34:55AM 8 (Exhibit Number PTX-162 was admitted.)

10:34:55AM 9 BY MR. COCHRAN:

10:34:57AM 10 Q. Dr. Rudnic, what support did the Oracea label provide to
10:35:00AM 11 your understanding of the Oracea's formulation?

10:35:03AM 12 A. Well, that Oracea meets each and every limitation of the
10:35:08AM 13 asserted claims.

10:35:09AM 14 Q. Can you walk us through this claim.

10:35:11AM 15 A. Sure. What you see on the left is Claim 1 of the Chang 740
10:35:15AM 16 patent and on the right is the label from Galderma. In Claim 1,
10:35:19AM 17 you can see it's an oral pharmaceutical composition of
10:35:22AM 18 doxycycline and --

10:35:23AM 19 THE COURT: Can I ask? Does anyone dispute that Oracea
10:35:31AM 20 does embody the Chang patents?

10:35:35AM 21 MR. COCHRAN: We don't.

10:35:37AM 22 MR. RAKOCZY: We have not disputed it.

10:35:38AM 23 THE COURT: I didn't think that was a dispute. You can
10:35:39AM 24 walk through lightly, but I can read the slide. I don't think
10:35:41AM 25 there's any dispute here about Oracea in the Chang patents.

10:35:50AM 1 MR. COCHRAN: well, there is some evidence I would like
10:35:51AM 2 to admit, then, Your Honor.

10:35:53AM 3 THE COURT: Okay. Please.

10:35:53AM 4 BY MR. COCHRAN:

10:35:59AM 5 Q. Let's turn to tab 15. This is PTX-175.

10:36:04AM 6 A. Yes.

10:36:05AM 7 Q. what is this document?

10:36:07AM 8 A. This is the clinical study report on multiple dose for
10:36:12AM 9 Oracea that was in their ANDA.

10:36:14AM 10 Q. Did you rely on this document in forming your opinions in
10:36:16AM 11 this case?

10:36:16AM 12 A. Yes.

10:36:18AM 13 MR. COCHRAN: Your Honor, Plaintiffs would like to
10:36:19AM 14 offer PTX-175 into evidence.

10:36:23AM 15 THE COURT: Any objection?

10:36:24AM 16 MR. RAKOCZY: No objection.

10:36:24AM 17 THE COURT: Admitted.

10:36:24AM 18 (Exhibit Number PTX-175 was admitted.)

10:36:24AM 19 BY MR. COCHRAN:

10:36:28AM 20 Q. Let's go to slide 39, please. Let's talk about Lupin's
10:36:36AM 21 product. First let's turn to PTX-198 in your exhibit book. This
10:36:40AM 22 is tab 16.

10:36:41AM 23 A. Yes.

10:36:42AM 24 Q. Do you recognize this document?

10:36:43AM 25 A. Yes.

1 Q. what is it?

2 A. This is the Lupin prescribing label that was in their ANDA.

3 Q. And did you rely on this document in forming your opinions
4 in this case?

5 A. Yes.

6 MR. COCHRAN: Your Honor, Plaintiffs would like to
7 offer 198 into evidence.

8 THE COURT: Any objection?

9 MR. RAKOCZY: No objection.

10 THE COURT: Admitted.

11 (Exhibit Number PTX-198 was admitted.)

12 THE COURT: Am I right there's no dispute there is oral
13 composition of doxycycline. That there is no dispute that there
14 is a once daily dosage with steady stream of .1 milligram and 1.0
15 and that there are excipients here?

16 MR. RAKOCZY: We do not dispute those facts, Your
17 Honor.

18 THE COURT: We can move over those things lightly, the
19 heart of this case is about is this 30:10 or --

20 MR. COCHRAN: Right. And I'd also like to point out
21 that there is no dispute that there is, in fact, an immediate
22 release portion and a delayed release.

23 THE COURT: There is no dispute that there is immediate
24 release portion. Now the size of those is in dispute.

25 MR. RAKOCZY: Exactly, Your Honor. Thank you. We

1 agree there's a 22 milligram immediate release and 18 milligram
2 delayed release, Your Honor.

3 THE COURT: Right.

4 MR. RAKOCZY: Their position is obviously the 18 has to
5 be segmented or understood differently.

6 BY MR. COCHRAN:

7 Q. Let's go on to slide 45 and let's talk a little bit more
8 about the design and function of Lupin's ANDA product.

9 Dr. Rudnic, what have you shown here on slide 46?

10 A. Well, this is a roadmap for what I'm going to talk about.

11 One, Lupin designed its ANDA product to have a weak enteric coat
12 and the design of that results in a 30:10 composition ratio. And
13 as a result their ANDA product infringes the Chang patents.

14 Q. Let's talk about how Lupin designed its ANDA product. On a
15 high level, how does Lupin manufacture its product?

16 A. You can see here it's a lot of unit operations, so it's a
17 fairly complicated process to manufacture. But basically can
18 come down to five stages, as Lupin calls it, sugar hardening
19 stage. You start coating on a sugar sphere, they harden that.
20 Then they load the drug, then they coat that and then they
21 enteric coat and they fill in capsules.

22 THE COURT: Why sugar? It just provides a useful kind
23 of like the nub of a pearl?

24 THE WITNESS: It's uniform, Your Honor. So the -- I've
25 done this quite a few times. If you try to create a pellet on

10:39:11AM 1 its own, they're rough, they don't always look spherical. These
10:39:16AM 2 sugar spheres are used in nonpareils in candy and confections.
10:39:21AM 3 And maybe as a child you might have seen them. And manufacturers
10:39:26AM 4 deliberately will take certain sieve sizes, certain particle size
10:39:32AM 5 cuts, so they're really quite tight in terms of particle size.

10:39:34AM 6 Now, when you coat spheres, what's really important is
10:39:38AM 7 particle size distribution. And so if you start with things that
10:39:41AM 8 are almost perfectly spherical and perfectly identical in terms
10:39:47AM 9 of size, at least you're starting from a good place.

10:39:47AM 10 BY MR. COCHRAN:

10:39:52AM 11 Q. I'd like to offer a few exhibits into evidence and I'll try
10:39:56AM 12 and shortcut this as much as possible. Let's turn to PTX-184,
10:40:01AM 13 Tab 17 in your witness book.

10:40:01AM 14 A. Yes.

10:40:03AM 15 Q. Do you recognize this document?

10:40:04AM 16 A. Yes.

10:40:05AM 17 Q. What is it?

10:40:05AM 18 A. This is the overall quality summary of the drug product from
10:40:10AM 19 the Lupin ANDA.

10:40:11AM 20 Q. Let's turn to the next tab, Tab 18. This is PTX-185.

10:40:16AM 21 Do you recognize this document?

10:40:17AM 22 A. Yes.

10:40:18AM 23 Q. What is it?

10:40:19AM 24 A. This is an excerpt from the product development report which
10:40:24AM 25 is known as 3.2.P.1 and basically it's a description and

10:40:31AM 1 composition of the drug product for Lupin's ANDA product.

10:40:33AM 2 Q. And did you rely on PTX-185 in forming your opinions in this
10:40:38AM 3 case?

10:40:38AM 4 A. Yes.

10:40:38AM 5 Q. Let's turn to the next tab, Tab 19. This is PTX-186.

10:40:42AM 6 Do you recognize this document?

10:40:43AM 7 A. I do.

10:40:44AM 8 Q. What is it?

10:40:45AM 9 A. This is the pharmaceutical development report for the Lupin
10:40:49AM 10 ANDA product.

10:40:51AM 11 Q. And did you rely on PTX-186 in forming your opinions?

10:40:56AM 12 A. I did.

10:40:56AM 13 Q. Let's go to Tab 20, PTX-187.

10:41:01AM 14 Do you recognize this document?

10:41:02AM 15 A. Yes.

10:41:03AM 16 Q. What is it?

10:41:03AM 17 A. This is the manufacturing process development and process
10:41:08AM 18 for Lupin's ANDA product.

10:41:10AM 19 Q. And did you rely on PTX-187 in forming your opinions in this
10:41:14AM 20 case?

10:41:15AM 21 A. I did.

10:41:16AM 22 MR. COCHRAN: Your Honor, Plaintiffs would like to
10:41:17AM 23 offer PTX-184, 185, 186, and 187 into evidence.

10:41:22AM 24 THE COURT: Mr. Rakoczy, any objection to any of those
10:41:24AM 25 four?

10:41:24AM 1 MR. RAKOCZY: No objection, Your Honor.

10:41:26AM 2 THE COURT: And am I right that 198 already got moved
10:41:28AM 3 in and admitted?

10:41:30AM 4 MR. COCHRAN: I believe you are right.

10:41:32AM 5 MR. RAKOCZY: Yes.

10:41:32AM 6 THE COURT: We've admitted everything apart from the
10:41:36AM 7 legal opinions and the Schneider article. Please proceed.

10:41:44AM 8 MR. COCHRAN: Thank you, Your Honor.

10:41:44AM 9 (Exhibit Numbers PTX-184, PTX-185, PTX-186, and
10:41:44AM 10 PTX-187 were admitted.)

10:41:44AM 11 BY MR. COCHRAN:

10:41:45AM 12 Q. So what, if anything, stands out to you about how Lupin
10:41:48AM 13 manufacturers its ANDA product?

10:41:50AM 14 A. Two things strike me immediately. Number one, the use of
10:41:54AM 15 methylene chloride and the percent weight gain at the enteric
10:41:58AM 16 coat stage.

10:41:59AM 17 Q. Why does methylene chloride concern you?

10:42:02AM 18 A. First of all, I worked with methylene chloride early in my
10:42:05AM 19 career. It smells awful. Anyone who's driven by a paint factory
10:42:10AM 20 in New Jersey before 1988, probably smelled it from I-95. But
10:42:16AM 21 methylene chloride has been found by the EPA to be an
10:42:20AM 22 unreasonable risk to human health.

10:42:22AM 23 It is not only that associated with neuro toxicity,
10:42:29AM 24 liver toxicity, cancer and even death. I worked at Bristol Myers
10:42:34AM 25 Squibb with a technician and he worked with methylene chloride a

1 long time before I got there and he died in his early 50s from
2 liver failure. Didn't drink. And we always thought it was due
3 to his exposure to methylene chloride and thankfully in the mid
4 '80s water based latex coatings and latex paint became available.
5 So by the late '80s, we switched over to water-based coatings.

6 THE COURT: So this was in common use?

7 THE WITNESS: Up until about 1984, Your Honor. And
8 then the EPA came out and said -- and it started with the states.
9 New Jersey was the first and then Washington state was the
10 second.

11 THE COURT: But this is the EPA. FDA hasn't done
12 anything about this?

13 THE WITNESS: They don't care, Your Honor.

14 THE COURT: Okay.

15 THE WITNESS: Sadly. Don't know. Call your
16 Congressman.

17 So I would tell you that this was very, very concerning
18 to me. Also the Centers For Disease Control consider this to be
19 an occupational carcinogen. And so, putting a carcinogen into a
20 pharmaceutical product raises a lot of questions and it was the
21 first thing I saw when I -- when you contacted me and I looked at
22 this. I said, why would they possibly use methylene chloride in
23 a pharmaceutical product today.

24 THE COURT: Is it common to use methylene chloride in
25 pharmaceutical coating processes in the United States?

10:44:10AM 1 THE WITNESS: Not in coating processes where you're
10:44:12AM 2 blowing it out the stack. And the other thing is --

10:44:14AM 3 THE COURT: What is it common for?

10:44:18AM 4 THE WITNESS: It is used in spray drying, Your Honor.
10:44:21AM 5 And spray drying is very -- very controlled, absolutely contained
10:44:26AM 6 environment. And they actually recover the solvent and reuse it.
10:44:32AM 7 Nothing goes out into the atmosphere. Nothing is being exposed
10:44:35AM 8 to the worker.

10:44:36AM 9 THE COURT: Right, but is it being ingested by the
10:44:38AM 10 person?

10:44:39AM 11 THE WITNESS: No, because by vacuum they can pull off
10:44:44AM 12 all the methylene chloride before it completely dries. Now, in
10:44:48AM 13 coating something different happens. So they will blow it out a
10:44:54AM 14 stack and they will use a scrubber to try to take out most of it.
10:45:00AM 15 Now scrubbers at their best are 99 percent.

10:45:04AM 16 THE COURT: How much is someone who is taking one of
10:45:06AM 17 these pill ingesting methylene chloride?

10:45:09AM 18 THE WITNESS: Trace amounts, Your Honor, but it's not
10:45:11AM 19 zero.

10:45:12AM 20 THE COURT: Right. And it's a lifetime drug?

10:45:13AM 21 THE WITNESS: And it's a lifetime drug. So contrast
10:45:17AM 22 that with Oracea where you have nothing but water-based coatings.
10:45:24AM 23 This is unnecessary. There was no reason to do this and so
10:45:28AM 24 knowing Oracea, knowing the fact that there's water-based
10:45:32AM 25 coatings, I look at this and I go, why would you put this kind of

10:45:36AM 1 material in a drug product when you don't have to.

10:45:40AM 2 And I was accused of being biased against Lupin because
10:45:45AM 3 of this. I said no, it just tells me this is an intentional
10:45:50AM 4 thing. I really hope it was intentional, you know.

10:45:53AM 5 THE COURT: So the basis of your finding of intent
10:45:56AM 6 that's the question raised. Keep saying they did this
10:46:00AM 7 intentionally, but it's not like you have any direct evidence
10:46:03AM 8 someone whispered or said it. It just looks crazy to you and
10:46:06AM 9 you're inferring from that?

10:46:08AM 10 THE WITNESS: Absolutely, Your Honor. My brain is
10:46:15AM 11 wired to do things safely and ethically and trying to treat
10:46:19AM 12 patients in a way that I don't put any harm to them. I am not
10:46:23AM 13 wired to think about what I need to do to succeed and maybe use a
10:46:31AM 14 material that I shouldn't be using. They shouldn't be using
10:46:36AM 15 this.

10:46:36AM 16 MR. RAKOCZY: Objection, Your Honor, relevance and this
10:46:38AM 17 is not anywhere in his reports.

10:46:41AM 18 MR. COCHRAN: He did talk about methylene chloride and
10:46:43AM 19 its effects on the workers and health risks in his expert report,
10:46:47AM 20 Your Honor.

10:46:48AM 21 MR. RAKOCZY: He's not testifying about health risks to
10:46:49AM 22 workers, Your Honor, he's now going into patients.

10:46:52AM 23 THE COURT: I am asking him what the basis is for
10:46:54AM 24 assertion of intent, because of skeptical, there was no direct
10:46:59AM 25 evidence of intent that -- he's answering why he has that in his

1 report. And so, you know, it's equivalent of responding to a
2 question on cross. I'm allowing it

3 MR. COCHRAN: Thank you, Your Honor.

4 BY MR. COCHRAN:

5 Q. Now Before we move on, let's turn to PTX-135 in your witness
6 book. This is Tab 221.

7 A. Yes. Got it.

8 Q. Do you recognize this document?

9 A. This is the excerpt from the CDC Centers For Disease Control
10 and website talking about methylene chloride.

11 Q. Did you rely on PTX-135 in forming your opinions in this
12 case?

13 A. Yes.

14 MR. COCHRAN: Your Honor, Plaintiffs would like to
15 offer 135 into evidence.

16 THE COURT: Any objection?

17 MR. RAKOCZY: Objection. Relevance, Your Honor. This
18 is not from the FDA. The FDA allows methylene chloride. They
19 have very strict controls for it. I don't see that this has
20 relevance.

21 THE COURT: I don't see what NIOSH. He touched
22 generally on this being the kind of subject but this seems little
23 far afield what NIOSH says about it.

24 MR. COCHRAN: Your Honor, this is from the CDC.gov
25 website. There's a URL at the bottom.

1 THE COURT: But it's about Occupational Safety &
2 Health.

3 MR. COCHRAN: This is something that he discussed in
4 his expert report.

5 THE COURT: I think this is getting a little far
6 afield. Keep it out on 403 grounds.

7 BY MR. COCHRAN:

8 Q. Let's turn to PTX-136. This is tab 22.

9 Do you recognize this document?

10 A. Yes. This is the EPA document that says methylene chloride
11 poses unreasonable risk to human health.

12 Q. Did you rely on 136 in forming your opinions?

13 A. Yes.

14 Your Honor, we would like to offer PTX-136 into
15 evidence.

16 MR. RAKOCZY: Same objection. Number one, relevance,
17 Your Honor. Number two, EPA has nothing to do with regulating
18 drug products in the United States. And in fact, what the EPA
19 says about methylene chloride, they specifically say does not
20 apply to drugs, which is solely the jurisdiction of the FDA.

21 MR. COCHRAN: There is relevance, Your Honor. This is
22 part of Dr. Rudnic's opinions that he presented in his opinion.

23 THE COURT: I believe he was discussing this in his
24 deposition and his report, correct? You're not saying this is
25 being sprung on us.

10:49:20AM 1 MR. RAKOCZY: No, no, Your Honor, I'm saying relevance,
10:49:23AM 2 number one. And number two, this is not anything to do with the
10:49:26AM 3 FDA and the regulation of drug products.

10:49:29AM 4 THE COURT: It's attenuated, but I will allow this as
10:49:34AM 5 something that he talked about in his report. I think you have
10:49:37AM 6 some very credible arguments that the weight I should give it is
10:49:42AM 7 very limited, but I will allow it to go to weight and not
10:49:45AM 8 admissibility.

10:49:47AM 9 MR. COCHRAN: Thank you, Your Honor.

10:49:47AM 10 (Exhibit Number PTX-136 was admitted.)

10:49:47AM 11 BY MR. COCHRAN:

10:49:50AM 12 Q. Now, Dr. Rudnic, did you form an opinion on why Lupin used
10:49:54AM 13 methylene chloride?

10:49:56AM 14 A. I am not sure why they used it, but the effect of using it
10:50:00AM 15 was interesting. You'll see that they start with a methylene
10:50:04AM 16 chloride coat in their sugar hardening stage. Then they go to a
10:50:08AM 17 water coat for the drug stage and then another methylene chloride
10:50:15AM 18 coat to seal the drug coat, followed by a water-based coat for
10:50:22AM 19 the enteric coat and then fill in capsules.

10:50:22AM 20 So they're stacking like on unlike coatings. Kind of
10:50:29AM 21 like a sandwich, with very different types of coatings. In my
10:50:34AM 22 view, you could argue this is to adequately seal the drug in the
10:50:41AM 23 sugar. This is not necessary -- or you know, Oracea does this
10:50:44AM 24 with water based coatings. So why you would select this
10:50:47AM 25 particular solvent. To do this became very questionable to me

10:50:53AM 1 until I saw this chart where I said, wow, they're stacking these.

10:50:58AM 2 And coatings are kind of interesting. It's kind of
10:51:02AM 3 like painting your wall with a latex paint. You wouldn't paint
10:51:06AM 4 it on wax paper, because it will just peel right off. well, when
10:51:10AM 5 you have a coating, the polymer has to be able to adhere to the
10:51:16AM 6 surface that it's being coated on or you'll have some space or
10:51:22AM 7 some lack of adhesion. And it's primarily because methylene
10:51:28AM 8 chloride and the kinds of things that -- the kinds of surfaces
10:51:33AM 9 that set up with solvents don't allow for the polymers on top of
10:51:38AM 10 it to actually penetrate and form a nice weave.

10:51:43AM 11 Q. Dr. Rudnic, do you have any evidence that this like and
10:51:46AM 12 unlike affects Lupin's pills?

10:51:50AM 13 A. I can see from scanning electron images that Lupin provided.
10:51:56AM 14 So here, you can see that with Oracea, which these are on the
10:52:00AM 15 top, you can notice that where the blue arrows are there -- you
10:52:05AM 16 can't see any difference between where the coating of -- you can
10:52:10AM 17 see the talc and polymer coating there.

10:52:13AM 18 You don't really see any difference between that and
10:52:16AM 19 what's below it where there's no talc, of white specs, Your
10:52:20AM 20 Honor. But you can see the coating and this is the lab scale
10:52:24AM 21 batch that we're going to talk about a in a minute, but at least
10:52:28AM 22 it's -- these images are instructive that even if this particular
10:52:33AM 23 batch questionable lab scale batch, you can see that there's
10:52:38AM 24 actual ridges of air that look like they occur in between one
10:52:44AM 25 coating and the other.

10:52:47AM 1 THE COURT: What is it that you understand to be air,
10:52:48AM 2 the small little circular pocket?

10:52:52AM 3 THE WITNESS: well, not just the circular pockets, Your
10:52:54AM 4 Honor. You can see that there seems to be -- so if you look at
10:52:57AM 5 the bottom left, you'll note bottom left figure, you'll notice
10:53:03AM 6 that the bottom arrow is pointing to an area between that talc
10:53:08AM 7 and enteric coat and the area underneath it. So this is what I
10:53:16AM 8 was saying about like applying paint to a wall. You want it to
10:53:20AM 9 adhere to the surface below. That is not adhering to what's
10:53:24AM 10 below it.

10:53:24AM 11 BY MR. COCHRAN:

10:53:25AM 12 Q. Let's turn to DTX-083. This is Tab 23.

10:53:32AM 13 Do you recognize this document?

10:53:34AM 14 A. Yes.

10:53:34AM 15 Q. Is this the report that these MVA amendments came from?

10:53:38AM 16 A. Yes.

10:53:38AM 17 MR. COCHRAN: Your Honor, Plaintiffs would like to
10:53:39AM 18 offer DTX-083 into evidence.

10:53:43AM 19 THE COURT: Any objection?

10:53:44AM 20 MR. RAKOCZY: No objection, Your Honor.

10:53:45AM 21 THE COURT: Admitted.

10:53:45AM 22 (Exhibit Number DTX-083 was admitted.)

10:53:45AM 23 BY MR. COCHRAN:

10:53:47AM 24 Q. Let's take a look at your next slide, Dr. Rudnic. What is
10:53:51AM 25 percent weight gain?

10:53:52AM 1 A. So percent weight gain is an average number. So if you were
10:53:56AM 2 to take pellet and before you started the coating process that
10:54:02AM 3 pellet was 100 percent of its weight. At the end of the coating
10:54:07AM 4 process, if it were 30 percent heavier, you would say that it had
10:54:12AM 5 a 30 percent weight gain.

10:54:15AM 6 Now this is important because in these coatings, and
10:54:20AM 7 we're talking specifically about the enteric coating. There's a
10:54:24AM 8 certain amount of that coating that is solid, principally the
10:54:30AM 9 polymer and other parts that are water. Now this particular
10:54:33AM 10 coating, Eudragit L30D55 is 30 percent solids. So 70 percent is
10:54:42AM 11 water, going to come off. And 30 percent are solid that are
10:54:47AM 12 going to be retained ideally on the pellet.

10:54:51AM 13 THE COURT: Come off when? During the manufacturing
10:54:53AM 14 process?

10:54:56AM 15 THE WITNESS: Spraying the coating.

10:54:58AM 16 THE COURT: It's like a latex paint?

10:55:00AM 17 THE WITNESS: Exactly, but instead of putting it on
10:55:03AM 18 with a brush or roller, you're spraying it on.

10:55:03AM 19 THE COURT: Got it.

10:55:07AM 20 And so what happens when you apply the coating to the
10:55:09AM 21 entire pellet population?

10:55:11AM 22 THE WITNESS: Ideally you would like the pellets to
10:55:13AM 23 be --

10:55:13AM 24 MR. RAKOCZY: Objection, Your Honor. This goes to our
10:55:16AM 25 objection on the entire bell curve, it's a cartoon. We have no

1 idea, there's no evidence if the bell curve looks like this, so
2 just renewing our earlier objection.

3 THE COURT: It's just a very general demonstrative or
4 cartoon. I don't think that it's admissible to prove anything
5 about the, you know, slope or shape or distribution or anything
6 like that. It's just illustrating the idea of some kind of
7 curve. And he's not saying it's precisely a normal distribution
8 or bell curve and I don't think he has a basis to say that.

9 MR. COCHRAN: That's right, Your Honor. This is just
10 an exemplary bell curve on the slide and Dr. Rudnic is going to
11 talk about what his opinion is on the distribution.

12 THE COURT: Okay. But I would also like to know what
13 the basis is for having a view of the distribution is that it is
14 a normal or bell curve distribution, if you have any evidence?

15 THE WITNESS: Actually, it could be a skewed
16 distribution as well, depending on a lot of different aspects.

17 THE COURT: If it's skewed then it's not a bell curve.

18 THE WITNESS: well, I understand that.

19 THE COURT: Strictly speaking a bell curve, as
20 mathematicians would talk about. This is just a figure of
21 speech?

22 THE WITNESS: It's less likely to be anything but a
23 bell curve because we start with a sphere, Your Honor.

24 THE COURT: I got it. And in nature lots of things
25 turn into bell curves but we don't really know?

10:56:36AM 1 THE WITNESS: It is -- I guess as a demonstrative the
10:56:39AM 2 point I'm trying to make, Your Honor, is that some of these
10:56:43AM 3 pellets will be less than the average and some of them will be
10:56:45AM 4 more than the average. I am not trying to make any more detailed
10:56:50AM 5 point than that.

10:56:52AM 6 THE COURT: Okay.

10:56:52AM 7 BY MR. COCHRAN:

10:56:53AM 8 Q. So let's go to your next slide. What have you shown here,
10:56:59AM 9 Dr. Rudnic?

10:57:00AM 10 A. Well, that in terms of particle size, the Lupin ANDA product
10:57:06AM 11 and the Oracea product use pellets that are presorted to be the
10:57:11AM 12 same particle size.

10:57:12AM 13 Q. And what weight gain would you expect for similar size
10:57:16AM 14 pellets?

10:57:18AM 15 A. You would have -- if they're similar size, you would expect,
10:57:22AM 16 given the same coating, you would expect the same weight gain.

10:57:26AM 17 Q. And did you look at the percent weight gain of Lupin
10:57:30AM 18 compared to Oracea?

10:57:31AM 19 A. Yes.

10:57:31AM 20 Q. What did you observe?

10:57:32AM 21 A. Well, I know that Lupin's is 18 percent. And what I'm about
10:57:39AM 22 to testify is that 18 percent is light and that you can tell from
10:57:46AM 23 the way it was selected that they selected the least possible
10:57:50AM 24 coating they could get away with. So if you just simply think --

10:57:54AM 25 THE COURT: You can't tell us the least possible they

10:57:57AM 1 could get away with. You can tell it's on the light side?

10:58:01AM 2 THE WITNESS: I am about to show you, Your Honor, it's
10:58:03AM 3 the least.

10:58:04AM 4 THE COURT: Okay.

10:58:05AM 5 THE WITNESS: So if it is the least, by logic some of
10:58:11AM 6 the pellets that are less coated than the average will be less
10:58:15AM 7 than weak.

10:58:19AM 8 MR. RAKOCZY: Objection, Your Honor, to that line of
10:58:21AM 9 testimony. And now showing, like I earlier objected to, we've
10:58:25AM 10 now got two bell curves with different numbers at the top
10:58:30AM 11 completely.

10:58:33AM 12 THE COURT: There's a basis for, but idea is they
10:58:33AM 13 overlap only a little bit and have normal distribution entailed.
10:58:38AM 14 I'm not seeing anything and I still have not heard an explanation
10:58:42AM 15 how it's the least. So I don't think you have a foundation for
10:58:45AM 16 any of that. So maybe you want to go back or have him testify
10:58:48AM 17 about how he knows it's less, the least possible.

10:58:52AM 18 THE WITNESS: Perhaps I can just get out one concept,
10:58:55AM 19 Your Honor, which is that a general principal in coating pellets
10:59:02AM 20 is that when you have a functional coat in a modified release
10:59:06AM 21 dosage form, the goal is to have as thick a coating as to ensure
10:59:11AM 22 that all of your pellets are robust. This is a general concept.

10:59:16AM 23 THE COURT: You are inferring from the fact it is so
10:59:19AM 24 much lighter, there was some kind of intent to do something out
10:59:23AM 25 of the ordinary?

10:59:24AM 1 THE WITNESS: And I will show you from data, Your
10:59:26AM 2 Honor, that I believe that.

10:59:27AM 3 THE COURT: Okay. Show me the data.

10:59:27AM 4 BY MR. COCHRAN:

10:59:30AM 5 Q. Let's go to your next slide, Dr. Rudnic. What have you
10:59:34AM 6 shown here?

10:59:34AM 7 A. Lupin, in their batch records, show that they have an
10:59:38AM 8 average weight gain of 18 percent at the enteric coating stage.
10:59:43AM 9 Oracea has a 30 percent weight gain at the enteric stage.

10:59:48AM 10 Q. Why is that important to you?

10:59:49AM 11 A. Well, because I have commercialized 6 other delayed release
10:59:53AM 12 products using Eudragit L30D55. Some of these were very, very
11:00:00AM 13 broadly big sellers. Adderall XR and others. And all of them
11:00:06AM 14 had more than 32 percent weight gain. Adderall XR had 40. So I
11:00:13AM 15 am used to this polymer being coated to about 32 to 40 percent.
11:00:19AM 16 So when I see 18 percent, that looks light to me. And so now I
11:00:25AM 17 am worried about how it functions and how it delivers.

11:00:30AM 18 Q. Okay. So how did Lupin select for that 18 percent weight
11:00:34AM 19 gain?

11:00:35AM 20 A. They did two things. They looked at in vitro testing and
11:00:39AM 21 they looked at their scanned electronic images but primarily in
11:00:46AM 22 vitro testing, quality control testing.

11:00:48AM 23 Q. Let's start with in vitro quality control testing. What did
11:00:54AM 24 they do?

11:00:54AM 25 A. This is a QC test at pH 1.1. This test is meant to be a

1 stress test on enteric polymer. So you put it at pH 1.1. Keep
2 it there for 2 hours and hope you don't see anything. And there
3 are limits for that. So what you notice is that on their
4 development batch, they started at a 17 percent weight gain and
5 then went up by 2 percent increments. And they saw leakage at 17
6 percent but did not see it at 19 or some of the other increasing
7 percentages. Then they took a scale batch and did the same
8 thing. Exposed it to the QC test for 2 hours at pH 1.1. And
9 what you see at 16 percent, they had leakage. But at 18 percent
10 and higher, they did not.

11 THE COURT: That's what you mean by the lowest?

12 THE WITNESS: So yeah. I think if 17 percent leaks and
13 16 percent leaks, 18 is about the lowest you can go and not see
14 leakage. And I just want to remind you that this QC test is a
15 mandatory pass for these kinds of products. So they have to pass
16 this test. And so for them, they selected the least thick
17 coating to pass the QC test.

18 THE COURT: Why is there anything improper about that?

19 THE WITNESS: Because if your least coating that will
20 show no leakage is 18 percent, and there are going to be some
21 pellets that are less than 18 percent because 18 percent is the
22 average, then that means some pellets are going to leak.

23 THE COURT: All right. But you don't have any evidence
24 as to whether this is a normal distribution, squished
25 distribution, flat distribution?

11:02:48AM 1 THE WITNESS: No. what I do have is data at a pH on
11:02:54AM 2 oral administration where I can show you that they do have
11:03:00AM 3 release.

11:03:00AM 4 BY MR. COCHRAN:

11:03:03AM 5 Q. Let's move on to your next slide. what do the SEM images
11:03:09AM 6 that Lupin provided you?

11:03:10AM 7 A. So these particular pellets, these scanning electron images,
11:03:15AM 8 were provided by Lupin. what you see is the development batch
11:03:19AM 9 that we talked earlier, 17 percent weight -- excuse me. This is
11:03:24AM 10 the -- yeah, this is the development batch, where they had 17
11:03:28AM 11 percent weight gain. And what you will notice between that and
11:03:32AM 12 19 percent weight gain is that in the 17 percent gain you see
11:03:36AM 13 some speckling there, that's talc in the coating. Talc has got a
11:03:41AM 14 certain diameter, and it's flaky and all sorts of stuff. So when
11:03:46AM 15 you don't have a very thick polymer coat, some of it tends to
11:03:50AM 16 stick out. well, this is important because talc is used in the
11:03:54AM 17 coating so that these acrylic coatings don't stick to one another
11:03:59AM 18 so you don't want that to happen because you might pull off some
11:04:02AM 19 of the coating and that kind of defeats the whole purpose. So
11:04:05AM 20 you put talc in it. That causes some imperfections. When you
11:04:10AM 21 see the speckling that you see in that, there's channels along
11:04:13AM 22 that talc because it doesn't adhere to the methacrylate coating.
11:04:19AM 23 And in those channels, drug can escape. So what you want to do
11:04:24AM 24 is have enough coating over and over so that you cover the talc
11:04:29AM 25 and that talc no longer can give you those channels. And that's

11:04:34AM 1 what you see at the 19 percent weight gain.

11:04:37AM 2 Q. Dr. Rudnic, let's turn to PTX-202. This is Tab 24. Do you
11:04:43AM 3 recognize it?

11:04:44AM 4 A. Yes, these are SEMs from scanned electron micrographs from
11:04:51AM 5 the Lupin ANDA.

11:04:55AM 6 Q. Are these the ANDA images you were just referring to?

11:04:57AM 7 A. Yes.

11:04:58AM 8 MR. COCHRAN: Your Honor, Plaintiffs would like to
11:04:59AM 9 offer PTX-202 into evidence.

11:05:02AM 10 THE COURT: Any objection?

11:05:02AM 11 MR. RAKOCZY: No objection, Your Honor.

11:05:04AM 12 THE COURT: Admitted.

11:05:04AM 13 (Exhibit Number PTX-202 was admitted.)

11:05:08AM 14 THE COURT: I think we should probably -- we have gone
11:05:11AM 15 quite a while, and I think it is appropriate to take a 10-minute
11:05:16AM 16 break and come back see if we can finish this up and take our
11:05:21AM 17 lunch break.

11:05:35AM 18 (Break from 11:05 a.m. until 11:17 a.m.)

11:17:43AM 19 THE COURT: You may resume.

11:17:44AM 20 MR. COCHRAN: Thank you, Your Honor.

11:17:44AM 21 BY MR. COCHRAN:

11:17:50AM 22 Q. So Dr. Rudnic, now that we have talked about how Lupin
11:17:55AM 23 designed its ANDA product, let's talk about how Lupin's product
11:18:00AM 24 functions. How does Lupin's product function?

11:18:02AM 25 A. I believe it functions as a 30:10 IR DR composition.

11:18:06AM 1 Q. And why do you say that?

11:18:09AM 2 A. Well, you can see that part of what they call their DR
11:18:15AM 3 portion actually releases immediately upon oral administration.
11:18:23AM 4 And I believe it's because of their thin and weak enteric coat.
11:18:29AM 5 And I believe that enteric coat is weak not only because of how
11:18:34AM 6 thin it is but also because it's on an unstable platform of a
11:18:39AM 7 methylene chloride coat.

11:18:41AM 8 Q. So how do you know all of this?

11:18:45AM 9 A. Well, there's two things. Mr. Avachat in his deposition
11:18:50AM 10 says so. And secondly, I can take a look at Lupin's data from
11:18:54AM 11 Lupin's ANDA that confirms those statements.

11:18:57AM 12 Q. And what did Mr. Avachat say?

11:19:00AM 13 A. Well, he said that the objective of their development was to
11:19:03AM 14 develop a product that's equivalent in all aspects to Oracea.
11:19:06AM 15 And when asked how he did that, he said they did whatever was
11:19:11AM 16 required by the regulation to be equivalent in all aspects.

11:19:15AM 17 Q. And what data did you rely on?

11:19:18AM 18 A. Well, I took a look at their ANDA and the in vitro
11:19:25AM 19 dissolution data at a biorelevant pH. This is also a QC test.
11:19:29AM 20 And in vivo bioequivalence data in the context of doxycycline
11:19:34AM 21 absorption window. And it was an objective of Lupin to obtain
11:19:39AM 22 the desired drug release rate in order to make this product
11:19:42AM 23 bioequivalence to Oracea using Mr. Avachat's words.

11:19:43AM 24 Q. And before moving on, can you remind us what the Kalantzi
11:19:48AM 25 article tells you?

11:19:49AM 1 A. well, Kalantzi says that the pH upon administration of a
11:19:53AM 2 drug product with water will give you a pH of about 4 and a half.
11:19:59AM 3 And as I said before, not only the Kalantzi article but common
11:20:05AM 4 sense tells if you have a pH of about 2, and you are taking an
11:20:09AM 5 equal volume of fluid at a pH of 7, the total fluid meets in the
11:20:13AM 6 middle at pH 4 and a half. So and there are other articles out
11:20:17AM 7 there that confirm that.

11:20:19AM 8 Q. So let's go to Slide 67. How did this relate to --

11:20:23AM 9 MR. RAKOCZY: Your Honor, I am going to object to the
11:20:25AM 10 last portion of the testimony. That's just yet another attempt
11:20:27AM 11 to try to wedge in the article that Your Honor excluded from
11:20:30AM 12 Schneider. He was not allowed to testify at his deposition and
11:20:34AM 13 instructed him not to answer. And he's now said twice other
11:20:38AM 14 articles.

11:20:39AM 15 MR. COCHRAN: He did not mention --

11:20:40AM 16 THE COURT: I am going to allow it. I am going to
11:20:42AM 17 allow it.

11:20:42AM 18 BY MR. COCHRAN:

11:20:44AM 19 Q. Let's go to Slide 67, Dr. Rudnic. How does that relate to
11:20:49AM 20 what Lupin did?

11:20:50AM 21 A. well, Lupin did exactly what the FDA requires them to do.
11:20:54AM 22 They administered 240 MLs of water with a test article either the
11:21:00AM 23 Lupin ANDA product or Oracea at the time of bioequivalence
11:21:09AM 24 testing.

11:21:10AM 25 Q. Let's go to PTX-194 in your witness book. This is Tab 25.

11:21:16AM 1 A. Yes.

11:21:17AM 2 Q. What is this document?

11:21:19AM 3 A. This is the clinical study report for the bioequivalence
11:21:25AM 4 study that I talked about.

11:21:26AM 5 Q. Did you consider PTX-194 in forming your opinions in this
11:21:30AM 6 case?

11:21:30AM 7 A. Yes.

11:21:31AM 8 MR. COCHRAN: Your Honor, Plaintiffs would like to
11:21:32AM 9 offer PTX-194 into evidence.

11:21:35AM 10 MR. RAKOCZY: No objection, Your Honor.

11:21:36AM 11 THE COURT: Admitted.

11:21:36AM 12 (Exhibit Number PTX-194 was admitted.)

11:21:36AM 13 BY MR. COCHRAN:

11:21:38AM 14 Q. Dr. Rudnic, what does the mean of this data 4.5 reveal?

11:21:44AM 15 A. The mean reveals they release exactly as Oracea which is
11:21:51AM 16 undisputed 30:10 IR DR product.

11:21:55AM 17 Q. And do you recall, Dr. Rudnic, that Lupin has accused you of
11:21:59AM 18 calling 150 minutes immediate release?

11:22:05AM 19 A. Well, this is a QC test. As I testified earlier and I am
11:22:12AM 20 testifying right now, the time frame in these QC tests is not
11:22:16AM 21 meant to mimic exactly the time frame in the body. It's a QC
11:22:22AM 22 test. And each test is trying to figure something out, so you
11:22:26AM 23 need to understand what it's trying to figure out. So in this
11:22:29AM 24 particular case, the capsules are kept at pH 1.1 for 2 hours.
11:22:37AM 25 This is a stress test. It's longer than the capsule will ever

11:22:41AM 1 reside in the stomach, so it has nothing to do with the time and
11:22:45AM 2 the stomach or release or other things. Your stomach does a much
11:22:50AM 3 better job of releasing than a USP dissolution apparatus. This
11:22:54AM 4 is a big test tube, if you will, and it's got a little stirrer in
11:23:02AM 5 there that revolves slowly.

11:23:05AM 6 THE COURT: This is a very strange graph. You say it's
11:23:09AM 7 pH 1.1 for 20 minutes but you don't report any data from 20
11:23:15AM 8 minutes to 60 minutes. You jump from 0 to 150.

11:23:20AM 9 THE WITNESS: I am about to show you the individual
11:23:21AM 10 data, Your Honor. What this shows you is that once you get to pH
11:23:26AM 11 4.5 -- and remember I said earlier that the FDA tells you for
11:23:31AM 12 these modified release products you should test at, in fact, they
11:23:34AM 13 want you to test at pH 4.5 all the way up to pH 7.5. So when you
11:23:41AM 14 do that -- and that's the first time that you are changing from
11:23:44AM 15 this pH 1.1 QC test to pH 4.5 QC test for another 2 hours, you
11:23:52AM 16 will see that you have identical release at the very first time
11:23:57AM 17 frame that Lupin takes a sample that happens to be at 30 minutes
11:24:02AM 18 after you have changed the buffer. Once you change the buffer,
11:24:06AM 19 it's like the clock starts over again. So this is 30 minutes
11:24:09AM 20 after you have now exposed it to a higher pH. Now recall, Your
11:24:14AM 21 Honor, that pH 1.1 is not a relevant pH in the stomach. It is
11:24:21AM 22 actually a pH that is supposed to be a stress test.

11:24:26AM 23 THE COURT: But the FDA expects you to use it.

11:24:29AM 24 THE WITNESS: Absolutely.

11:24:30AM 25 THE COURT: You have used the 1.1 on your own

11:24:32AM 1 medicines?

11:24:33AM 2 THE WITNESS: without a doubt, Your Honor. And it's a
11:24:35AM 3 useful QC test. But understand that whatever it releases in 2
11:24:39AM 4 hours does not equilibrate to whatever releases in the stomach
11:24:45AM 5 for those 2 hours.

11:24:46AM 6 The other thing to remember is that the polymer that's
11:24:48AM 7 being used here, and as the counsel for Lupin points out, it's
11:24:55AM 8 the same polymer. So the polymer in Oracea and the polymer in
11:24:59AM 9 Lupin's ANDA product is a product from Evonik called Eudragit
11:25:08AM 10 L30D55. Tough to say but German. What do you expect?

11:25:14AM 11 In that particular polymer, it has ammonium groups in
11:25:20AM 12 the acrylic acid side chains. These ammonium groups will ionize
11:25:29AM 13 at a certain pH 5.5. All right. And so if you hold it at pH
11:25:35AM 14 1.1, nothing should ionize, nothing should come out, and that's
11:25:41AM 15 why the QC test is so important. But as you start to go up
11:25:45AM 16 higher in pH and you come close to 5.5, about 5, the polymer will
11:25:50AM 17 start to ionize and will start to flake off and dissolve at pH
11:25:56AM 18 5.5, which is the pH in the duodenum.

11:25:59AM 19 THE COURT: Can you explain why that's the case?

11:25:59AM 20 THE WITNESS: Sure.

11:26:03AM 21 THE COURT: I mean, for someone who's not a chemist, it
11:26:05AM 22 makes far more sense that a more acidic environment would cause
11:26:08AM 23 it to dissolve. But we're not extremely acidic or extremely
11:26:13AM 24 basic. We're at something in between. Why is it dissolving more
11:26:17AM 25 easily at a moderate pH?

11:26:19AM 1 THE WITNESS: So this is the crux of enteric polymers,
11:26:23AM 2 Your Honor. So for something to go into solution, it needs to be
11:26:30AM 3 ionized. In other words, water, which is an ionic type solvent
11:26:37AM 4 likes ionic things. If it's not ionic, in other words, if it's
11:26:41AM 5 not ionized at all, it will sit there like cement. And this is
11:26:47AM 6 what the FDA wants to see from an enteric polymer. Put it in
11:26:52AM 7 there for 2 hours, we should see nothing. So this is a stress
11:26:56AM 8 test. You can leave it there for a day. I had Adderall XR
11:27:00AM 9 samples over a weekend. Nothing. And that was much more sizable
11:27:06AM 10 compound than this one. So the polymer itself at 1.1 is locked
11:27:12AM 11 down. You should see no release which is why, when I look at the
11:27:19AM 12 way that they selected the 18 percent weight gain, it was the
11:27:24AM 13 least possible percentage they could without seeing any release
11:27:30AM 14 at that pH 1.1. So then I don't know. You can keep it for 1
11:27:35AM 15 hour, 2 hours, 12 hours, doesn't matter. That polymer is locked
11:27:39AM 16 down. But as the pH starts to go up, the ammonium groups start
11:27:45AM 17 to become ionized. Once they're ionized --

11:27:48AM 18 THE COURT: Because ammonium is basic and --

11:27:52AM 19 THE WITNESS: That's right, Your Honor. Once you get
11:27:54AM 20 to higher pH, the ammonium groups ionize and then it starts to
11:27:59AM 21 flake off. So it's a very clever thing. And Eudragit was
11:28:08AM 22 created by a German company. It basically replaced shellac, and
11:28:15AM 23 I'm serious about this, in the pharmaceutical industry.

11:28:20AM 24 THE COURT: You mean shellac?

11:28:20AM 25 THE WITNESS: Yes, Your Honor.

1 And shellac also ionizes and dissolves at higher pHs.
2 Anybody who's ever varnished a boat knows it will last for only a
3 certain amount of time and after a while it will flake off. So
4 this is better than shellac. Okay?

5 So the idea is that these QC tests are meant to test
6 the integrity of this coating. And so what the FDA wants you to
7 do is, okay, let's start testing at 4.5 because we know that a
8 lot of these enteric coatings are designed to start releasing at
9 5.5. We should see no release at 4.5 because it's not ionized
10 and we shouldn't see release.

11 Then they want you to test it at 5 or 5.5. And I think
12 they say 4.5 or go to 6.5. But they want to see a range of pH
13 between 4.5 and 7.5. That's in an FDA guidance document 20 years
14 old that I helped do for modified-release dosage forms. So
15 anyway, so this testing basically tests the integrity and
16 ionization of these polymers.

17 BY MR. COCHRAN:

18 Q. Dr. Rudnic, before we move on, did you create this graph on
19 this slide 68?

20 A. No.

21 Q. Who did?

22 A. Lupin.

23 Q. Let's go to your next slide and walk to the individual data.
24 Go ahead.

25 A. Okay. So what you see here is dissolution data from Lupin's

1 ANDA. So these are Lupin's data but they are comparing
2 themselves, the ANDA product, with Oracea.

3 Q. What have you shown here in the green box?

4 A. So what we show here is the initial part of this QC test
5 where you have pH 1.1. And you see it runs for 2 hours. And
6 what you will notice is that 55 percent of the Lupin's ANDA
7 product is the immediate release pellet. So here their immediate
8 release pellets are doing exactly what they are supposed to do.
9 They are releasing. Doxycycline is soluble at pH 1.1 so it comes
10 off very easily. You will notice that Oracea, which has 75
11 percent or 30 milligrams of doxycycline, releases almost entirely
12 its amount of immediate release pellets. So again, their
13 immediate release pellets are doing exactly what they are doing.
14 Both sets of immediate release pellets are releasing 100 percent
15 of what they should be releasing. So no problem. No question
16 here. This is exactly as you would expect.

17 Q. Let's move on to the next part of the slide.

18 A. So this is very interesting. So what you will notice is
19 that this test then moves to pH 4.5. And remember, the time
20 frames in this QC test have nothing to do with correlations to
21 exactly in the GI tract. It's a QC test. And so what you have
22 here in Oracea in green, no additional release from the Oracea.

23 THE COURT: I am trying to understand these figures
24 because you would have thought that the numbers would keep going
25 up as more time passed yet on the bottom we have some lower

11:32:00AM 1 numbers after 150, 180 minutes.

11:32:05AM 2 THE WITNESS: Slightly lower. And it may be due to
11:32:08AM 3 changing and eliminating some of the solution while adding in
11:32:13AM 4 some buffer.

11:32:14AM 5 THE COURT: Oh, okay. Yeah.

11:32:17AM 6 THE WITNESS: But the important thing here, Your Honor,
11:32:19AM 7 is that you are not getting additional release above what has
11:32:24AM 8 already been released. In other words, the delayed release
11:32:28AM 9 pellets of Oracea that are coated with Eudragit L30D55 are not
11:32:37AM 10 releasing at pH 4.5. They are coated at 30 percent. However,
11:32:42AM 11 pellets that are coated at 18 percent are releasing. In fact,
11:32:46AM 12 all of them release a little bit and 5 of the 12 capsules are
11:32:50AM 13 releasing quite a bit. And this is --

11:32:52AM 14 THE COURT: Numbers 1, 3, 6, 7, and 8?

11:32:58AM 15 THE WITNESS: Correct. And you can see at the end of
11:33:00AM 16 this QC test, the average release is 75 percent. 75 percent of
11:33:04AM 17 40 milligrams is 30 milligrams, Your Honor.

11:33:07AM 18 THE COURT: Okay. Got it.

11:33:12AM 19 THE WITNESS: This should not happen if you have a good
11:33:17AM 20 robust enteric coat of Eudragit L30D55. We don't see this with
11:33:24AM 21 Oracea. We do see this with the Lupin product. And I will
11:33:27AM 22 remind Your Honor, these data are from Lupin's ANDA. They
11:33:32AM 23 certified to the FDA that these data were accurate, they were
11:33:36AM 24 reliable, and they were released by the quality assurance unit.
11:33:42AM 25 If these data were unexpected, in fact, if they looked at these

11:33:49AM 1 compared to Oracea and they thought they had a problem, they were
11:33:52AM 2 legally obligated to do an investigation. They were legally
11:33:56AM 3 obligated to do a retest. They didn't.

11:33:59AM 4 THE COURT: Okay. This is about the FDA. Got it. I
11:34:03AM 5 understand that. The Court still has to decide how that bears on
11:34:06AM 6 the meaning of the patent.

11:34:07AM 7 THE WITNESS: Understood, Your Honor. I just want to
11:34:11AM 8 talk about the function of their product, and I am using their
11:34:13AM 9 data to do it.

11:34:13AM 10 BY MR. COCHRAN:

11:34:15AM 11 Q. Dr. Rudnic, what's the standard number of capsules that
11:34:18AM 12 should be tested in vitro dissolution test?

11:34:21AM 13 A. Typically no less than 6, and 12 if you want to do an
11:34:25AM 14 instant repeat. So 12 is a more robust number than 6.

11:34:30AM 15 Q. Does this impact your opinion at all?

11:34:34AM 16 A. It solidifies my opinion that their so-called DR pellets are
11:34:39AM 17 releasing at a pH 4.5 which is a pH, as I testified, that you
11:34:43AM 18 will see in the stomach upon immediately upon oral
11:34:47AM 19 administration.

11:34:48AM 20 THE COURT: But you are saying this 150 figure, is that
11:34:53AM 21 after 120 minutes of pH 1.1 plus 30 minutes of 4.5?

11:34:58AM 22 THE WITNESS: Yes.

11:35:00AM 23 THE COURT: Okay. So then for immediate for the
11:35:03AM 24 immediate release, I should be looking at that row of 150 where
11:35:06AM 25 the mean is 64 percent. 64 percent of 40 milligrams is about

11:35:17AM 1 two-thirds. what is that? Like 26, 27?

11:35:21AM 2 THE WITNESS: Yeah. So Your Honor, 30 milligrams, 30
11:35:25AM 3 minutes into this test is not 30 minutes immediate release in the
11:35:30AM 4 body. The time frames have no --

11:35:33AM 5 THE COURT: I see. This is 30 minutes in vi tro but you
11:35:36AM 6 are saying in vi vo it probably looks different.

11:35:39AM 7 THE WITNESS: It almost certainly would. And the point
11:35:42AM 8 is that a lot of the release that you see in vi vo especially in
11:35:52AM 9 the various parts of the intestinal tract are not correlated to
11:35:55AM 10 these tests. These tests were never meant to tell you minute by
11:35:59AM 11 minute how much --

11:36:00AM 12 THE COURT: Quality control test. I got it.

11:36:04AM 13 THE WITNESS: So it's important for us to understand
11:36:05AM 14 the limitations of these tests. These are not meant to be
11:36:10AM 15 completely indicative of what you will see in the body. So but
11:36:17AM 16 what this does tell you, the information this test does tell you
11:36:21AM 17 is that it releases 30 milligrams when it should only be
11:36:25AM 18 releasing 22 milligrams. That's what these data tell me.

11:36:25AM 19 BY MR. COCHRAN:

11:36:30AM 20 Q. Now, Dr. Rudnic, did Dr. Buckton and Ms. Gray attempt to
11:36:35AM 21 discredit these data?

11:36:36AM 22 A. They did.

11:36:38AM 23 Q. what is your understanding of their argument?

11:36:41AM 24 A. well, they called something called a hotspot. I mean, this
11:36:48AM 25 is a ghost. This is not scientific. No one has ever proven that

1 it exists. Certainly nobody has ever proven that it can impact
2 the way Eudragit L30D55 dissolves.

3 Q. Dr. Rudnic, what is a hotspot?

4 A. I am not sure. But from what they are talking about, it
5 means that when you change the buffer, somehow all of this basic
6 buffer ended up at the capsule and somehow it just blew up. This
7 is not supported by science.

8 Q. Let's talk about that a little bit and let's go to PTX-223
9 in your witness book. This is Tab 26.

10 THE COURT: Perhaps you can also explain what exactly
11 the hotspot theory is to understand what you are rejecting.

12 THE WITNESS: I will do my best, Your Honor. I am sure
13 Dr. Buckton and Ms. Gray will probably have their own version of
14 this. But I will tell you what I think it is. So you can --
15 when you have acid buffer in that QC test at pH 1.1 and you want
16 to change it to pH 4.5, you have to do that by adding something
17 with a higher pH. So when you do that, there has to be some
18 mixing that occurs for it to become uniform. Before it becomes
19 uniform, there may be spots where some of the pH is low and some
20 of the pH is high. I will concede that that might happen for a
21 second or two or 10 seconds but not for tens of minutes. And no
22 one has ever shown that it actually exists to have an effect. My
23 personal theory is that this is an excuse to retest a bad batch.
24 So people generally don't like to fail a batch or recall a batch
25 so they are desperate to find a reason to retest it. I believe a

1 hotspot is a convenient excuse. That's my personal opinion.

2 BY MR. COCHRAN:

3 Q. Dr. Rudnic, let's look at the Miller paper.

4 A. This paper in PTX-223 was written by someone named Dave
5 Miller. And he was a student, graduate student in Bill Williams'
6 lab at the University of Texas. I know both of them. I used to
7 work with Dave Miller, and I used to work with Bill Williams. So
8 what's interesting about this paper is that Dave -- and I didn't
9 know this about Dave until we got into this case. But Dave had
10 done some work using nuclear magnetic resonance technology. Lots
11 of words there, but what it means is that they looked at the
12 molecular basis of whether or not these things would mix quickly.
13 And they looked at molecules, not just general pHs.

14 And what they found is that the mixing occurs pretty
15 much within seconds and that no difference in either slow -- so
16 they did one slow where it took maybe 10, 15 minutes. And they
17 did one normally and showed that there's no difference between
18 the dissolution of this enteric polymer Eudragit L30D55 whether
19 it's slow or fast.

20 And the important thing here is that you have to
21 remember there's 12 vessels that this analyst has to cover. They
22 have 5 minutes, according to the USP method, to get that buffer
23 into all 12. Wow. So you can imagine. You stop this and now
24 you have 5 minutes to get the aliquot into each of these 12
25 vessels. You better be quick. So they are probably more likely

1 to be on the quick side than the slow side. So whatever it takes
2 to equilibrate these two pH media will happen in seconds. And
3 that's what the Miller paper shows.

4 Q. Dr. Rudnic, did you rely on PTX-223 in forming your
5 opinions?

6 A. I did.

7 MR. COCHRAN: Your Honor, Plaintiffs would like to
8 offer PTX-223 into evidence.

9 THE COURT: Any objection?

10 MR. RAKOCZY: No objection, Your Honor.

11 THE COURT: Admitted.

12 MR. COCHRAN: Thank you.

13 (Exhibit Number PTX-223 was admitted.)

14 BY MR. COCHRAN:

15 Q. Was Ms. Gray able to identify a hotspot in the Miller paper?

16 A. No.

17 Q. What did she say?

18 A. She said a lot of things but she just circled the whole page
19 so the whole thing was a hotspot.

20 Q. What does that tell you?

21 A. Well, there's no hotspot. And you can see at the bottom of
22 the vessel where the capsules reside, quite uniform.

23 Q. And what other challenges did Dr. Buckton and Ms. Gray make
24 to the data presented?

25 A. To be charitable, this is a questionable batch of --

11:41:58AM 1 MR. RAKOCZY: Objection, Your Honor. This is opinions
11:42:02AM 2 we saw nowhere in his reports.

11:42:04AM 3 THE COURT: But this is for purposes of rebuttal. I
11:42:06AM 4 mean, we technically could bring him back after the testimony.
11:42:10AM 5 And it certainly seems more efficient to allow rebuttal now if
11:42:15AM 6 that's acceptable to the parties.

11:42:18AM 7 MR. COCHRAN: I would also mention that this was all
11:42:19AM 8 discussed in Dr. Rudnic's deposition.

11:42:21AM 9 THE COURT: I'm going to allow it rather than having to
11:42:24AM 10 bring him back in a day and a half.

11:42:28AM 11 MR. RAKOCZY: Understood, Judge.

11:42:29AM 12 THE WITNESS: Thank you, Your Honor. So Lupin had an
11:42:34AM 13 opportunity to retest the existing ANDA batch, the one that was
11:42:42AM 14 submitted to the ANDA. I mean, they had 230,000 capsules. I
11:42:45AM 15 imagine they had a few of those laying around. And my
11:42:49AM 16 understanding is that their excuse for not testing is, oh, it
11:42:53AM 17 expired 2 months ago. Well, an interesting thing is that if they
11:42:58AM 18 had tested, they could have extended the expiration date. So
11:43:02AM 19 merely testing it again would have extended the expiration date.
11:43:06AM 20 I don't believe they wanted to retest that ANDA batch.

11:43:09AM 21 THE COURT: That's speculation. Go on.

11:43:11AM 22 THE WITNESS: I will move on to say, Your Honor, the
11:43:14AM 23 batch they made in response to this litigation differs
11:43:21AM 24 considerably from their ANDA batch. It is 6,000 capsules versus
11:43:27AM 25 240,000 capsules. The FDA would mandate you to do bioequivalence

11:43:34AM 1 test because the size of these batches are so different.

11:43:37AM 2 THE COURT: How do you know that the air flow particle
11:43:40AM 3 dynamics of the polymer enteric spray rate were different for
11:43:45AM 4 this batch? What tells you that?

11:43:47AM 5 THE WITNESS: There are two batch records that I looked
11:43:49AM 6 at. One that was given to us a couple days ago which is the
11:43:54AM 7 batch record for this batch and one from their ANDA. So I can
11:43:58AM 8 look at all of these things. The spray rate is 10 fold. The air
11:44:05AM 9 flow is 10 fold. I mean, I don't know what could be. The other
11:44:10AM 10 thing is that their justification for this was that the
11:44:15AM 11 manufacturer of the coating equipment says, well, there's a
11:44:18AM 12 general scale-up parameter.

11:44:23AM 13 THE COURT: So you're criticizing their samples but you
11:44:25AM 14 didn't run any tests yourself.

11:44:28AM 15 THE WITNESS: So Your Honor, the manufacturer says that
11:44:33AM 16 that scale-up parameter that they used could vary by up to 20
11:44:37AM 17 percent, plus or minus 20 percent. So there's a lot of wiggle
11:44:42AM 18 room here. And I have done scale-up my whole life, and I can
11:44:45AM 19 tell you that you have to do a lot of different iterations in the
11:44:49AM 20 process to figure out how they affect things.

11:44:52AM 21 THE COURT: So they didn't do it well, but you didn't
11:44:54AM 22 do it at all.

11:44:55AM 23 THE WITNESS: I didn't have to, Your Honor. And the
11:44:58AM 24 reason why I say I didn't have to is because you look at the
11:45:00AM 25 performance of products to figure out if they are the same.

11:45:07AM 1 THE COURT: You are looking at functionally how it
11:45:09AM 2 works in vivo in blood streams but that's like outputs, not
11:45:15AM 3 inputs. Got it.

11:45:17AM 4 THE WITNESS: Sure. So the in vitro data at pH 4.5 is
11:45:21AM 5 different between the ANDA batch that they submitted to the FDA
11:45:27AM 6 and this batch which they didn't submit to the FDA and they
11:45:31AM 7 didn't do bioequivalence testing. So what's going to happen is
11:45:36AM 8 you are going to see some of the experts for Lupin get up and
11:45:39AM 9 talk about how this batch is the same as the ANDA. It is not, in
11:45:42AM 10 my opinion. It is different in terms of the way it's
11:45:45AM 11 manufactured. And it functions -- it performs differently from
11:45:49AM 12 based on the in vitro data. So for those things alone, I say
11:45:53AM 13 it's different in a lot of different ways. And it would take a
11:45:57AM 14 lot of research and a lot of time to figure out exactly how.

11:45:57AM 15 BY MR. COCHRAN:

11:46:03AM 16 Q. Let's go back to the data. What have you shown here?

11:46:08AM 17 A. These are the plasma time curves for the Lupin ANDA product.

11:46:14AM 18 THE COURT: We have a preserved Daubert objection here.
11:46:17AM 19 It's understood. It's preserved for the record. But I am
11:46:22AM 20 allowing this.

11:46:24AM 21 MR. RAKOCZY: Thank you, Your Honor.

11:46:24AM 22 THE WITNESS: Your Honor, it might be helpful if I
11:46:27AM 23 explain what you are looking at. So these are plasma time curves
11:46:31AM 24 or blood level curves in the vernacular of the bioequivalence
11:46:38AM 25 study that was performed by Lupin. These are Lupin data. So

11:46:41AM 1 what you have on the left is a standard plot. And that same
11:46:47AM 2 data, the same set of data are plotted in a semi-log plot on the
11:46:54AM 3 right.

11:46:54AM 4 So semi-log plots take out any difference, so we will
11:46:57AM 5 forget that for the moment. If you look at the chart on the
11:47:02AM 6 left, what you see are two very similar curves. Now, for
11:47:11AM 7 bioequivalence, what the FDA looks at are two measurements. One
11:47:18AM 8 is the C-max or the peak concentration. So the peaks that you
11:47:23AM 9 see pretty much at around 4 hours, 5 hours there. That point
11:47:31AM 10 represents where the absorption of a drug product equals the
11:47:38AM 11 elimination of the drug product.

11:47:40AM 12 THE COURT: Show me which peaks you are talking about.
11:47:42AM 13 The peak of the line at 6 hours on the left-hand graph?

11:47:47AM 14 THE WITNESS: If you look at the left side of the left,
11:47:49AM 15 you see the highest data points.

11:47:52AM 16 THE COURT: Mean concentration so the highest blood
11:47:54AM 17 concentration is getting 450 on the left-hand side and scale on
11:48:01AM 18 the right.

11:48:02AM 19 THE WITNESS: That's harder to read. But if you go to
11:48:05AM 20 about 450 on the left side, you can see that that is the C-max,
11:48:13AM 21 maximum concentration for both the Lupin ANDA product and Oracea.
11:48:20AM 22 Now, the FDA takes that measurement, C-max and says that is a
11:48:26AM 23 measure of the rate of drug absorption and release of a dosage
11:48:33AM 24 form.

11:48:34AM 25 THE COURT: There's some in vivo similarity here. The

1 FDA cares about it. But it's not dispositive of the patent.

2 THE WITNESS: I will leave that, Your Honor. I just
3 want to finish my testimony that it is hard, very hard to be
4 statistically the same for both the C-max and the area under this
5 curve; two measurements for bioequivalence. And they did that
6 not only for fasted but fed, a doubly-hard standard.

7 So these products match both the rate and extent of
8 drug absorption. Not my opinion. It's the FDA's opinion. Now,
9 because the FDA says that these bioequivalence studies matter in
10 terms of release of a drug substance, I can come to the
11 conclusion that the Lupin ANDA product looks quite similar to a
12 known and proven 30:10 IR DR.

13 THE COURT: By the way, is the reference product here
14 the Oracea and the test product is Lupin's?

15 THE WITNESS: Correct. It's hard to make out because
16 the graphs are so similar.

17 THE COURT: Right. Okay.

18 BY MR. COCHRAN:

19 Q. Dr. Rudnic, let's go to PTX-190 in your witness book. This
20 is Tab 27. Do you recognize this document?

21 A. Yes.

22 Q. What is it?

23 A. This is Lupin's bioequivalence fasting study of doxycycline
24 capsules that created the data that we just saw.

25 Q. And did you consider PTX-190 in forming your opinions in

11:50:23AM 1 this case?

11:50:23AM 2 A. Yes.

11:50:25AM 3 MR. COCHRAN: Your Honor, Plaintiffs would like to
11:50:26AM 4 offer PTX-190 into evidence.

11:50:29AM 5 THE COURT: Any objection?

11:50:30AM 6 MR. RAKOCZY: No objection, Your Honor.

11:50:31AM 7 THE COURT: Admitted.

11:50:31AM 8 (Exhibit Number PTX-190 was admitted.)

11:50:31AM 9 BY MR. COCHRAN:

11:50:33AM 10 Q. So Dr. Rudnic, moving on to your next slide, what have you
11:50:37AM 11 concluded from the data in Lupin's own ANDA?

11:50:41AM 12 A. Doxycycline's narrow absorption window requires a specific
11:50:46AM 13 ratio of IR DR. I know this from the Oracea NDA, all the studies
11:50:52AM 14 that they did in developing Oracea. The scintigraphic study that
11:51:00AM 15 I talked about. 30:10 is what's needed. And you can't get off
11:51:03AM 16 far from 30 milligrams IR and still be bioequivalence to Oracea.
11:51:10AM 17 That is very clear from the data in the Oracea NDA. What I
11:51:13AM 18 showed just recently is that Lupin's doxycycline has a so-called
11:51:22AM 19 DR component but 8 milligrams or 75 percent in total or 30
11:51:28AM 20 milligrams gets released at a pH immediately following oral
11:51:32AM 21 administration. And 22 milligrams plus 8 milligrams equals 30.
11:51:38AM 22 So I am testifying today that I believe Lupin's doxycycline
11:51:43AM 23 product is a 30 milligram IR 10 milligram DR.

11:51:49AM 24 THE COURT: Dr. Rudnic, let me go back to a basic
11:51:54AM 25 anatomical question. Say you take an average pill like the kind

11:51:56AM 1 you develop. You told me from the time you ingest a pill with
11:52:00AM 2 what, a quarter liter of water, to the time it makes it to the
11:52:04AM 3 bottom of the stomach the polymer is about an hour?

11:52:08AM 4 THE WITNESS: Yes.

11:52:09AM 5 THE COURT: Can you generalize about how long that pill
11:52:11AM 6 spends in the duodenum, how long it spends in the jejunum, the
11:52:14AM 7 ilium, and the colon. Is there like a standard figure or a range
11:52:18AM 8 of figures that you were to ballpark it?

11:52:21AM 9 THE WITNESS: Sure. So the duodenum probably about an
11:52:27AM 10 hour and a half.

11:52:29AM 11 THE COURT: So 1.5 hours in duodenum.

11:52:33AM 12 THE WITNESS: It could be less. It could be less if
11:52:35AM 13 there were food moving it along.

11:52:37AM 14 THE COURT: So some drugs are instructed to take with
11:52:40AM 15 food, and that's going to affect it. And others you are told
11:52:43AM 16 don't take it within a couple of hours of a meal.

11:52:45AM 17 THE WITNESS: That's this one.

11:52:46AM 18 THE COURT: This one is don't take with food.

11:52:48AM 19 THE WITNESS: That's right.

11:52:49AM 20 THE COURT: If you don't take it with food, how long
11:52:51AM 21 does it spend in the duodenum?

11:52:53AM 22 THE WITNESS: Probably about an hour at the most.

11:52:56AM 23 THE COURT: Up to one hour if no food. Okay.

11:53:01AM 24 THE WITNESS: And then comes the jejunum and ilium.
11:53:05AM 25 And that depends, but that could be anywhere from 2 hours to 6

11:53:11AM 1 hours.

11:53:12AM 2 THE COURT: 2 to 6 hours assuming you haven't ingested
11:53:16AM 3 food right then?

11:53:17AM 4 THE WITNESS: That's right.

11:53:18AM 5 THE COURT: And then the colon.

11:53:19AM 6 THE WITNESS: And then the colon. It could be in the
11:53:21AM 7 colon for a day or two. And it depends on again food. So mother
11:53:28AM 8 nature is pretty good at getting rid of waste and food, so it
11:53:32AM 9 moves things along if you have a lot of --

11:53:35AM 10 THE COURT: Right. So your testimony was that the
11:53:37AM 11 absorption rate is very high in the duodenum like in the 80s.

11:53:37AM 12 THE WITNESS: Yes.

11:53:44AM 13 THE COURT: And then falls to the 30s. I don't know if
11:53:44AM 14 it was 37 or --

11:53:50AM 15 THE WITNESS: Almost 90 percent in the duodenum. And
11:53:50AM 16 about 37 --

11:53:54AM 17 THE COURT: 37. So 37, 38 in the ilium in the jejunum
11:53:58AM 18 but there's up to an hour for the medicine to be ingested into
11:54:00AM 19 the duodenum. So you know there's bioequivalence in terms of how
11:54:05AM 20 long it lasts and the figures were for, you know, hour, hour and
11:54:10AM 21 a half at a pH of 4.5 or whatever. But you can't say like at
11:54:15AM 22 what point in the duodenum this is all dissolving. what's the pH
11:54:19AM 23 in the duodenum?

11:54:21AM 24 THE WITNESS: 5.5, Your Honor.

11:54:24AM 25 THE COURT: 5.5. Stomach you said there was a range,

11:54:26AM 1 you said 3 was like --

11:54:27AM 2 THE WITNESS: Anywhere from 2 to 5, and let's call it 3
11:54:31AM 3 in the middle.

11:54:32AM 4 THE COURT: 2 to 5 pH. And then 5.5 pH in duodenum.
11:54:40AM 5 And what would you say the pH is in jejunum and ilium?

11:54:44AM 6 THE WITNESS: Jejunum probably about 6. Slightly
11:54:48AM 7 higher.

11:54:51AM 8 THE COURT: And the ilium?

11:54:52AM 9 THE WITNESS: About 6 and a half to 7 depending on what
11:54:56AM 10 kind of diet you typically have. High fiber diets are slightly
11:55:04AM 11 higher.

11:55:06AM 12 THE COURT: These figures are going to hold basically
11:55:08AM 13 true for medicines that are not ingested with food.

11:55:08AM 14 THE WITNESS: That's correct.

11:55:12AM 15 THE COURT: That's helpful. I do not have the benefit
11:55:18AM 16 of premed or biochem background. Thank you.

11:55:18AM 17 THE WITNESS: Understood, Your Honor. You're welcome.

11:55:18AM 18 BY MR. COCHRAN:

11:55:22AM 19 Q. Dr. Rudnic, what's the current status of Lupin's ANDA at the
11:55:28AM 20 FDA?

11:55:29AM 21 A. It is tentatively approved.

11:55:33AM 22 Q. Let's go to PTX-049, Tab 28.

11:55:33AM 23 A. Yes.

11:55:34AM 24 Q. Do you recognize this document?

11:55:35AM 25 A. I do.

11:55:35AM 1 Q. what is it?

11:55:36AM 2 A. It's the tentative approval letter from the FDA to Lupin for
11:55:40AM 3 their ANDA.

11:55:42AM 4 Q. Did you consider PTX-049 in forming your opinions in this
11:55:47AM 5 case?

11:55:47AM 6 A. I did.

11:55:48AM 7 MR. COCHRAN: Your Honor, Plaintiffs would like to
11:55:50AM 8 enter PTX-049 into evidence.

11:55:53AM 9 THE COURT: Any objection?

11:55:53AM 10 MR. RAKOCZY: No objection.

11:55:54AM 11 THE COURT: Admitted.

11:55:54AM 12 (Exhibit Number PTX-049 was admitted.)

11:55:54AM 13 BY MR. COCHRAN:

11:55:56AM 14 Q. All right. Let's go to your next slide. what conclusions
11:55:59AM 15 have you drawn based on all the data and Lupin's own ANDA?

11:56:02AM 16 A. My conclusion is that Lupin's ANDA product infringes the
11:56:06AM 17 Chang patents.

11:56:07AM 18 Q. Let's talk about your opinions on infringement. Let's go to
11:56:11AM 19 the next slide. Can you walk us through this claim in relation
11:56:15AM 20 to your --

11:56:17AM 21 A. This is claim one of the Chang 532 patent, and you can see
11:56:20AM 22 that it starts as an oral pharmaceutical composition of
11:56:25AM 23 doxycycline. And on the right, I have Lupin's label and you can
11:56:28AM 24 see doxycycline for oral use and it's 40 milligrams once daily.

11:56:37AM 25 THE COURT: We can go through 076, 077, 078. None of

11:56:44AM 1 those is really in dispute. why don't we go to 079.

11:56:48AM 2 MR. COCHRAN: Understood, Your Honor.

11:56:48AM 3 BY MR. COCHRAN:

11:56:53AM 4 Q. what are we showing here?

11:56:54AM 5 A. This is Claim 1 of the Chang 532 patent. Again, composition
11:56:58AM 6 consisting of an immediate release IR portion comprising a drug
11:57:02AM 7 wherein the drug consists of about 30 milligrams doxycycline. My
11:57:08AM 8 contention and my testimony today is that because they have a
11:57:16AM 9 like unlike layering of coatings which in my view is a fragile
11:57:23AM 10 platform and a very light weight gain, they have designed a
11:57:30AM 11 product that will leak, and it leaks at pH 4.5 which is where you
11:57:37AM 12 are going to see the pH at the time of oral administration. They
11:57:45AM 13 release 30 milligrams of doxycycline at that pH. 75 percent of
11:57:50AM 14 the product. And the in vivo data they have is remarkably
11:57:57AM 15 similar bioequivalence data to Oracea and undisputed 30:10 IR DR
11:58:02AM 16 product.

11:58:03AM 17 Q. In your opinion, does Lupin's ANDA product meet this claim
11:58:08AM 18 limitation?

11:58:08AM 19 A. Yes.

11:58:09AM 20 Q. Let's move on to the next slide. Have you formed an opinion
11:58:12AM 21 on whether this claim element is met under the doctrine of
11:58:16AM 22 equivalents?

11:58:17AM 23 A. Yes, it's insubstantially different from a pharmaceutical
11:58:20AM 24 composition containing a 30 milligram IR portion.

11:58:22AM 25 Q. why do you say that?

11:58:24AM 1 A. well, it functions in substantially the same way to achieve
11:58:29AM 2 substantially the same result. And the function is that it
11:58:32AM 3 releases 30 milligrams of doxycycline immediately on oral
11:58:36AM 4 administration to alter subject's steady state blood levels. And
11:58:42AM 5 the way it does it is about 8 milligrams of doxycycline in the DR
11:58:46AM 6 portion is intentionally and immediately released by Lupin's thin
11:58:49AM 7 and weak enteric coat. The result of all this is that their ANDA
11:58:53AM 8 product functions as a 30 milligram IR 10 milligram DR in the
11:58:58AM 9 body that is equivalent to Oracea.

11:59:02AM 10 THE COURT: Can I ask? Is there anything done to pills
11:59:04AM 11 to cause them to linger in the duodenum or jejunum or ileum
11:59:09AM 12 longer than they otherwise would or do they all pass at roughly
11:59:14AM 13 the same rate?

11:59:15AM 14 THE WITNESS: There are actual polymers, Your Honor,
11:59:16AM 15 that can be added to the surface of either capsules or pellets
11:59:20AM 16 that are what we call bioadhesive. And they tend to be some
11:59:26AM 17 cellulose derivatives and some others. This is a poly
11:59:33AM 18 methacrylic acid copolymer. There's some acrylic acid versions
11:59:38AM 19 that are also bioadhesive.

11:59:41AM 20 THE COURT: It can be done but there's no reason to
11:59:42AM 21 think that was done here.

11:59:46AM 22 THE WITNESS: Absolutely not, Your Honor. And
11:59:47AM 23 generally, the idea if you want to slow things down, pellets are
11:59:50AM 24 good because they tend to get into the folds of the intestinal
11:59:54AM 25 tract. And if they're somewhat adhesive, they go slower. So

12:00:00PM 1 they never really suck onto the intestines; they'll just go
12:00:02PM 2 slower.

12:00:02PM 3 THE COURT: Because the absorption rate for a lot of
12:00:05PM 4 meds is higher earlier in the intestinal tract. You might want
12:00:11PM 5 it to go slower.

12:00:14PM 6 THE WITNESS: So a big, big effort in the 1990s and
12:00:16PM 7 early 2000s was bioadhesion and what they call gastro retentive
12:00:25PM 8 dosage forms, there's a whole company formed on this, where the
12:00:27PM 9 idea was to get the release so far high up you would hit all the
12:00:31PM 10 absorption windows and get higher bioavailability. By and large,
12:00:35PM 11 they have not succeeded. Mother nature is a lot smarter than we
12:00:42PM 12 chemists are.

12:00:43PM 13 THE COURT: I don't know if it matters whether you're
12:00:46PM 14 eating roughage or not.

12:00:48PM 15 THE WITNESS: Food is going to move things along.

12:00:48PM 16 BY MR. COCHRAN:

12:00:50PM 17 Q. Dr. Rudnic, in your opinion, does Lupin's product infringe
12:00:55PM 18 this claim under the doctrine of equivalents?

12:01:01PM 19 A. Yes, it does.

12:01:02PM 20 Q. Let's move on to the next slide. What do they show here?

12:01:05PM 21 A. This is Claim 1 of the Chang 532 patent. Showing that it
12:01:11PM 22 has a delayed release or DR portion wherein the drug consists of
12:01:15PM 23 about 10 milligrams of doxycycline.

12:01:18PM 24 Q. And in your opinion, does Lupin's ANDA product infringe this
12:01:22PM 25 claim element?

1 A. It does because as I testified, I believe that 8 milligrams
2 is released as an IR portion to join the 22 milligrams of IR
3 pellets to be 30 milligrams of IR. In a 40 milligram dosage
4 form, that leaves 10 milligrams. And what you see is that is at
5 a time other than immediately following oral administration.

6 Q. Have you formed an opinion on whether this claim element is
7 met under the doctrine of equivalents?

8 A. Yes.

9 Q. What is that opinion?

10 A. Is that it does infringe on the doctrine of equivalents
11 because it is insubstantially different from a pharmaceutical
12 composition containing 10 milligram DR portion.

13 Q. Why do you say that?

14 A. Well, it has the same function and substantially the same
15 way to achieve substantially the same result. The function is
16 that it releases 10 milligrams of doxycycline at a time other
17 than immediately following oral administration and about 8
18 milligrams of doxycycline in that what is called DR portion is
19 intentionally and immediately released by Lupin's thin and weak
20 enteric coat. This leaves 10 milligrams to be released at a time
21 other than immediately following oral administration. The result
22 of all this is that Lupin's ANDA product functions as a 30
23 milligram IR 10 milligram DR product in the body that is
24 bioequivalence to Oracea, an undisputed 30 milligram IR 10
25 milligram DR product.

12:02:55PM 1 Q. In your opinion, does Lupin's product infringe this claim
12:02:58PM 2 element under the doctrine of equivalents?

12:03:01PM 3 A. It does.

12:03:02PM 4 Q. And --

12:03:03PM 5 THE COURT: We can skip 085 and 086.

12:03:07PM 6 MR. COCHRAN: You read my mind, Your Honor.

12:03:07PM 7 BY MR. COCHRAN:

12:03:12PM 8 Q. Let's go to Slide 87. Dr. Rudnic, what have you shown here?

12:03:18PM 9 A. So this is Claim 15. I mentioned before this is a method
12:03:21PM 10 claim for treating rosacea which is a form of acne in a human if
12:03:28PM 11 you consider the dependent Claim 16. And you can see that
12:03:32PM 12 Lupin's ANDA product infringes literally and under the doctrine
12:03:35PM 13 of equivalents. And the composition parts of that claim we have
12:03:40PM 14 already discussed at length.

12:03:42PM 15 THE COURT: It's the same for the methods as for Claim
12:03:47PM 16 1; correct?

12:03:48PM 17 THE WITNESS: Yes, Your Honor.

12:03:49PM 18 THE COURT: So the key here is going to be -- well,
12:03:53PM 19 that's the end of the 532. And then on the 740, we can go
12:03:57PM 20 straight to Slide 91. Your analysis on the 740 patent of the
12:04:03PM 21 30:10 ratio is going to be the same for the 740 as for the 532;
12:04:08PM 22 correct?

12:04:09PM 23 THE WITNESS: You are correct, Your Honor.

12:04:10PM 24 THE COURT: And then your analysis of the function and
12:04:12PM 25 the doctrine of equivalents on 93 is the same for the 740 and the

12:04:17PM 1 532?

12:04:18PM 2 THE WITNESS: You are correct, Your Honor.

12:04:18PM 3 THE COURT: And I don't know if there's anything you
12:04:20PM 4 want to say about Slide 94 about the delayed release. Is this
12:04:24PM 5 the same as what we saw earlier or do you need to say anything
12:04:28PM 6 further about this?

12:04:29PM 7 THE WITNESS: It is the same, Your Honor.

12:04:31PM 8 THE COURT: 94, 95, 96, the gelatin, the excipients,
12:04:37PM 9 the coatings. So there's the method claim is the same on the 740
12:04:42PM 10 and the 532; right?

12:04:44PM 11 THE WITNESS: Correct, Your Honor.

12:04:45PM 12 THE COURT: Was there anything else you needed to add
12:04:47PM 13 about differences in the method claims or differences in the 740?
12:04:53PM 14 BY MR. COCHRAN:

12:04:53PM 15 Q. One quick question. Dr. Rudnic, if we can go back one
12:04:58PM 16 second? This will be very quick. Go back to Slide 98. Can you
12:05:11PM 17 remind us what Lupin's ANDA product is indicated for?

12:05:15PM 18 A. It's indicated for the treatment of rosacea.

12:05:20PM 19 Q. Thank you.

12:05:20PM 20 THE COURT: And rosacea is a kind of skin disorder,
12:05:25PM 21 isn't it?

12:05:25PM 22 THE WITNESS: Sure. The most notable patient that
12:05:28PM 23 suffers from rosacea is former President Clinton, Your Honor. So
12:05:33PM 24 if you see Mr. Clinton, often his face is red. And a lot of
12:05:39PM 25 people suggest that's because he's imbibing. It's not. It's

12:05:43PM 1 because he suffers from rosacea. Rosacea is a form of acne.
12:05:47PM 2 It's really like little red dots in your skin which cause your
12:05:50PM 3 face to look red. So doxycycline, like most of the tetracyclines
12:05:58PM 4 at low doses, very low doses, has an antiinflammatory effect.

12:06:04PM 5 THE COURT: Does anyone understand why that is?
12:06:06PM 6 Because people thought this was a subtherapeutic dose.

12:06:10PM 7 THE WITNESS: well, it's a subtherapeutic dose for an
12:06:11PM 8 antibiotic. But most antibiotics, almost all of them,
12:06:15PM 9 amoxicillin and others, at the very lowest of their doses are
12:06:20PM 10 somewhat anti-inflammatory. The problem is, if you were to give
12:06:25PM 11 them every day for the rest of your lives, you would probably get
12:06:28PM 12 a superinfection and resistant bacteria and all sorts of things.

12:06:31PM 13 THE COURT: You think the max level at 1.0 microgram
12:06:36PM 14 seems to work?

12:06:37PM 15 THE WITNESS: It does. So you're maximizing over the
12:06:40PM 16 course of a day the anti-inflammatory effect for rosacea but not
12:06:45PM 17 triggering the antibiotic effect which as we know causes all
12:06:49PM 18 sorts of problems.

12:06:51PM 19 THE COURT: Sorry. I know you crafted your direct
12:06:58PM 20 examination very well and very carefully. Is there anything else
12:07:00PM 21 you want to add?

12:07:01PM 22 MR. COCHRAN: No, Your Honor.

12:07:28PM 23 (Lunch break at 12:07 p.m.)
24
25

C E R T I F I C A T I O N

I certify that the foregoing is a correct transcript
from the record of proceedings in the above-entitled matter.

/s/ Bobbie J. Shanfelder

Bobbie J. Shanfelder, RDR, CRR

Official Court Reporter

Date: January 9, 2024

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